Tailored Expectant Management in Reproductive Medicine

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The art of medicine consists in amusing the patient while nature cures the disease.
Voltaire.

Aan mijn ouders

CONTENTS

CHAPTER 1

Introduction and outline of this thesis

INTRODUCTION

Subfertility is defined as a failure to conceive after at least one year of regular unprotected intercourse (Zegers-Hochschild et al. 2009). It affects approximately 10% of couples in their reproductive lives (Boivin et al. 2007; Gnoth et al. 2003). The incidence of subfertility is increasing in the developed world mainly due to postponement of maternity. After a basic fertility work up about 25% of couples is diagnosed with unexplained subfertility, 30% with a mild male factor, 5% with a severe male factor, 20% with an ovulation disorder and in 20% of the couples other diagnoses as tubal factor, cervical subfertility, endometriosis and sexual disorders are made (Brandes et al. 2010; Collins and Van 2004).
In couples with unexplained or mild male subfertility the first step in the treatment cascade is often intra uterine insemination (IUI) with or without ovarian stimulation (OS). If 6-9 cycles of IUI with ovarian stimulation do not lead to a live birth (Custers et al. 2008), the second step in the treatment cascade for these couples is often In vitro fertilisation (IVF) (ESHRE 2008; NVOG: national guideline subfertility 2011).

Intra Uterine Insemination

The rationale for performing IUI is that motile spermatozoa are concentrated in a small volume and inseminated directly into the uterine cavity close to the released oocyte, bypassing the cervix. The aim of ovarian stimulation is to increase the number of oocytes available for fertilisation and to optimise timing of insemination. The first scientifically described homologous insemination dates from 1799, where the author describes how a man with severe hypospadias collected his semen in a syringe and introduced it into the vagina of his wife. The insemination was successful (Hogerzeil 1997).
The first publication of a randomised clinical trial on intra uterine insemination in couples with poor semen quality was in 1984 (Kerin et al. 1984). This 3-armed trial compared IUI on the day of the luteinising hormone surge with intercourse in which timing was based on either the luteinising hormone surge or on the basal body temperature. After 39 inseminations, 8 women conceived. Intra uterine insemination was more successful than LH-timed intercourse (0/38; $p<0.05$) and natural intercourse timed by the basal temperature curves (1/34; $p = 0.022$).

Since this first randomised controlled trial (RCT) on IUI, the number of IUI treatments with and without ovarian stimulation has increased rapidly. However, no national or international registrations are available concerning the exact number of treatments and pregnancy rates. One retrospective study estimated that 28,500 IUI cycles were performed in the Netherlands in 2003 with an ongoing pregnancy rate of 7% per cycle and with a multiple pregnancy rate of 9% (Steures et al. 2007c).
The first Cochrane review was published in 2000 on IUI with or without ovarian stimulation (OS) for couples with male subfertility included 3,662 completed cycles and concluded that

IUI offers couples with male subfertility benefit over timed intercourse (TI), both in natural cycles (combined odds ratio with 95% confidence intervals: 2.4, 1.5 - 3.8) and in cycles with OS (combined odds ratio with 95% confidence intervals: 2.1, 1.3 - 3.5). Intrauterine insemination in cycles with OS improved the probability of conception compared with IUI in natural cycles but significance was not reached (Odds Ratio (OR) with 95% confidence intervals (CI): 1.7, 0.98 - 3.2). So, the authors concluded that intra-uterine insemination offered couples with male subfertility benefit over timed intercourse, both in natural cycles and in cycles with COH. In case of a severe semen defect (with more than 1 million motile sperm after semen preparation) IUI in natural cycles should be the treatment of first choice, but the value of COS needed to be further investigated in RCTs. (Cohlen et al. 2000).

The most recent update of this Cochrane review on IUI for male subfertility was performed in 2007. For the comparison IUI versus timed intercourse both in natural cycles no evidence of difference between the probabilities of pregnancy rates per woman after IUI was found (OR 5.3, 95% CI 0.42 to 67). No statistically significant difference between pregnancy rates per couple for IUI with OS versus IUI could be found (OR 1.4, 95% CI 0.92 to 2.3). For the comparison of IUI versus TI both in stimulated cycles there was also no evidence of a statistically significant difference in pregnancy rates per couple either (OR 1.6, 95% CI 0.83 to 3.3). There were insufficient data available for adverse outcomes such as OHSS, multiple pregnancy, miscarriage rate and ectopic pregnancy to perform a statistical analysis. They concluded that there was insufficient evidence of effectiveness to recommend or advice against IUI with or without OS above TI, or vice versa. The authors thus recommended that large, high quality randomised controlled trials, comparing IUI with or without OS with pregnancy rate per couple as the main outcome of interest needed to be performed before firm conclusions can be drawn (Bensdorp et al. 2007).

A recent update of a Cochrane review on IUI for couples with unexplained subfertility was published this year. One trial compared IUI in a natural cycle with expectant management and showed no evidence of increased live births (334 women: OR 1.6, 95% CI: 0.92 to 2.8). In the six trials where IUI was compared with TI, both in stimulated cycles, there was evidence of an increased chance of pregnancy after IUI (six RCTs, 517 women: OR 1.68, 95% CI 1.1 to 2.5). A significant increase in live birth rate was found for women where IUI with OS was compared with IUI in a natural cycle (four RCTs, 396 women: OR 2.0, 95% CI 1.2 to 3.5). The trials provided insufficient data to investigate the impact of IUI with or without OS on several important outcomes including live births, multiple pregnancies, miscarriage and risk of ovarian hyperstimulation. There was no evidence of a difference in pregnancy rate for IUI with OS compared with TI in a natural cycle (two RCTs, total 304 women: data not pooled). The final comparison of IUI in natural cycle to TI with OS showed a marginal, significant increase in live births for IUI (one RCT, 342 women: OR 1.9, 95% CI 1.1 to 3.4). Data on multiple pregnancies and other adverse events for treatment with OS were insufficient to allow conclusions (Veltman-Verhulst SM et al. 2012).

In general, the two Cochrane reviews discussed above, concluded that the quality of the included trials was poor, the sample sizes were small, and complications like multiple pregnancies were poorly reported and more well-designed and well powered studies are necessary.

In Vitro Fertilisation

IVF was introduced for couples who are infertile due to tubal occlusion. Lesley Brown, the first woman ever to give birth after IVF had severe tubal pathology after several failed surgical procedures. In the next decennia after the birth of Louise Brown in 1978, IVF turned out to be effective in women with tubal pathology (Steptoe et al. 1980). In 1992 IVF with Intra Cytoplasmatic Sperm Injection (ICSI) was developed for men with very poor semen quality failing to fertilize in vitro (Palermo et al. 1992). In ICSI, fertilization is induced by directly injecting a motile, normally formed sperm cell into the oocyte. In couples with severe tubal pathology and severely impaired semen quality it is nearly impossible to achieve fertilization in vivo and these couples are thus dependent on IVF or ICSI to have a chance of pregnancy. Approximately 20% of all couples with an unfulfilled child wish are at present diagnosed with one of these two indications (Collins and Van 2004; van der Steeg et al. 2007a; Brandes et al. 2011).

In 1990 around 50% of all patients treated with IVF were diagnosed with a tubal factor (Annual reports 1990-2010 AMC & VUmc 2010). Although the absolute number of patients with a tubal factor remained stable, in 2010 this group accounted for just 10-12% of all IVF patients (Annual reports 1990-2010 AMC & VUmc 2010). Over the years the indications for IVF have thus been widely broadened.

At present, more than half of all IVF/ICSI treatments are performed in couples with unexplained or mild male subfertility, leading to an increase in the total number of IVF cycles performed (Brandes et al. 2010). Over the past 13 years the number of IVF cycles has risen by more than 50% in the Netherlands (Kremer et al. 2008a). The number of IVF cycles in Europe has doubled in the period between 1997-2006 (de Mouzon et al. 2010). In 2009, one in every 39 newborns in the Netherlands originated from IVF or ICSI treatment (www.lirinfo.nl). In 2012 the mean ongoing pregnancy rate per cycle was 19% for IVF and 23% for ICSI (www.nvog.nl 2011).

In contrast to couples with a tubal factor or very poor semen quality, couples with unexplained or mild male subfertility still have a chance of natural conception (Brandes et al. 2010). Empirical data proving the effectiveness of IVF/ICSI over coitus for these indications are scarce. Randomised controlled trials comparing IVF/ICSI for these indications with expectant management or IUI with or without OS are limited to small-scale trials with heterogeneous patient groups (Goverde et al. 2000; Hughes et al. 2004; Reindollar et al. 2010).

A systematic Cochrane review with meta-analysis concluded that the added value of IVF in relation to expectant management or IUI with or without OS in couples with unexplained subfertility has not been proven, due to paucity of data: only one trial study with 51 women

compared IVF with expectant management and the live birth rate per woman was significantly higher with IVF (45.8%) than expectant management (3.7%) (OR 22, 95% CI 2.5 to 189). There were no comparative data for comparing IVF with the use of clomiphene citrate. There was no significant difference in live birth rate between IVF (40,7%) and IUI alone (25,9%) (OR 1.9, 95% CI 0.88 to 4.3, 1 RCT, 113 women). In studies comparing IVF versus IUI with OS, live birth rate per woman did not differ significantly between the groups among treatment-naive women (OR 1.0, 95% CI 0.74 to 1.5, 2 RCTs, 234 women) but was significantly higher in a large RCT of women pre-treated with clomiphene citrate IUI (OR 2.6, 95% CI 1.9 to 3.6, 1 RCT, 341 women). These three studies could not be pooled due to high heterogeneity (I(2) = 84%). There was no evidence of a significant difference in multiple pregnancy rate or ovarian hyperstimulation syndrome (OHSS) between the two treatments (OR 0.64, 95% CI 0.31 to 1.2, 3 RCTs, 351 women; OR 1.5, 95% CI 0.25 to 9.4, 1 RCT, 118 women, respectively). The authors concluded that IVF may be more effective than IUI+SO but due to paucity of data from RCTs the effectiveness of IVF for unexplained infertility relative to expectant management, clomiphene citrate and IUI alone remains unproven. Adverse events and the costs associated with these interventions have not been adequately assessed (Pandian et al. 2012). In a cohort of newly referred subfertile couples, the contribution of IVF in couples with unexplained subfertility was extremely limited, with ongoing pregnancy rates of 13%, compared with 45%, 45% and 37%, respectively for patients with tubal factors, endometriosis and severe male factors (Brandes et al. 2010).

One of the causes for the increase in the number of IUI and IVF cycles is modern reproductive behaviour. The average age at which women give birth for the first time is increasing on a yearly basis. At the same time, the average age of women requiring medical aid at the clinic for assisted reproduction is increasing every year (de Mouzon et al. 2010; Kremer et al. 2008a). Women's pregnancy chances are decreasing from the age of 30. From the age of 35 there is a severe drop and from the age of 40 the chances of pregnancy are very low (Hunault et al. 2004). Modern assisted reproduction techniques cannot compensate for this "ovarian aging" – the pregnancy chances with assisted reproductive techniques also decrease with age – as does the in vivo conception (Templeton 2000; Lintsen et al. 2007).

Expectant management

In couples without a major cause for their unfulfilled child wish expectant management may be a good option. In a large cohort study concerning subfertile couples with unexplained subfertility, 74% of all pregnancies was conceived naturally (Brandes et al. 2011). The problem is how to identify the couples that would benefit from expectant management, since gynaecologists differ widely in estimating fertility prognoses in subfertile couples, prognostic models may be of help here (van der Steeg et al. 2007a). For several treatment policies, prognostic models have been developed. For eight models, the validity was assessed in populations other than the one in which the model was developed (external validation),

and only three of these showed good performance (Leushuis et al. 2009). One model predicting the chance of natural conception had reached the phase of impact analysis (Hunault et al. 2004). This impact analysis showed that in couples with an intermediate chance of natural conception (between 30%-40% chance of live birth within 12 months), IUI with OS had no beneficial effect on live birth rate compared to expectant management (Steures et al. 2006). Based on these results our national guideline concerning fertility treatment recommends an expectant management for 6-12 months in couples with a intermediate or good prognosis (>30% chance of natural conception), so called tailored expectant management (TEM) (NVOG: national guideline subfertility 2011).

BACKGROUND OF THIS THESIS

Implementation of tailored expectant management

It is unclear how TEM is implemented, but large cohort studies suggest poor implementation (Kremer et al. 2008a; Mourad et al. 2008; van der Steeg et al. 2007a). Optimal implementation of expectant management for 6-12 months for subfertile couples with good chances of natural conception can cause a reduction in healthcare costs without compromising live birth rates. Besides a cost reduction, optimal implementation of TEM is likely to lead to a lower number of multiple pregnancies. Even though multiple pregnancy rates per treatment cycle are decreasing, the risks are still substantially higher than those in natural conceptions. Multiple pregnancies are associated with a higher morbidity and mortality in both mothers and neonates (Helmerhorst et al. 2004). Finally, fertility treatments carry a significant physical and psychological burden (Verberg *et al.*, 2008;Verhaak *et al.*, 2002;Verhaak *et al.*, 2007).
To improve the implementation of TEM a systematic approach is needed including acquisition of data of current practice; identification of potential determinants; analysis of barriers and facilitators for the implementation, development of an implementation strategy and finally an evaluation of the implementation strategy (Grol and Grimshaw 2003; Kremer et al. 2008a). In the first part of this thesis we performed the first steps of this systematic implementation study to improve the implementation of TEM in subfertile couples with unexplained or male subfertility. In a prospective cohort study we evaluated the adherence to tailored expectant management and we identified risk factors for non-adherence to tailored expectant management. Subsequently we identified patients' and professionals' barriers and facilitators of TEM and its´ influence on patients' appreciation of TEM and professionals' adherence to TEM. Finally, we developed an implementation strategy to improve the implementation of tailored expectant management based on our previous findings.

Applicability of prognosis of natural conception

The second part of this thesis is twofold. First we compared a selection strategy based on prognosis of natural conception with a funding based selection strategy used in New Zealand. In New Zealand public funding for fertility treatment is restricted to subfertile women who are unlikely to conceive naturally, based on clinical and social criteria known as the clinical priority access criteria (CPAC-score). In this study this CPAC score was compared with the prognostic model developed in the Netherlands (the Hunault model) in a New Zealand cohort of 663 couples.

Second, we aimed to explore the capacities of prognostic models to select couples for IUI or IVF. At the moment prognostic models are not used to select couples for fertility treatment. As evidence from randomised trials underpinning the use of fertility treatments like IUI with or without OS and IVF in couples with unexplained or male subfertility is poor, international guidelines differ in their recommendations concerning specific treatment strategies. However, most guidelines recommend starting with less invasive treatments (without OS) and moving on to more aggressive interventions if these are unsuccessful or when the woman is older and the duration of subfertility is longer (The Practice Committe of the American Society of Reproductive Medicine 2012; NICE 2004; ESHRE 2001). Data from RCTs are contradictory and occasionally counterintuitive (Bhattacharya et al. 2008; Goverde et al. 2000; Guzick et al. 1999; Hughes et al. 2004; Reindollar et al. 2010; Soliman et al. 1993a; Steures et al. 2006). A possible explanation for this may be the inclusion of couples with varying prognostic profiles as evident from wide ranges in female age and duration of subfertility. As a result, the prognosis of the included couples could be quite heterogeneous with respect to their chances of natural conception.

To test our hypothesis, we performed an individual-patient data analysis of published RCT's, and evaluated whether couples' prognosis of natural conception attenuated or strengthened the impact of assisted reproduction. Authors of published randomised trials comparing expectant management (EM), intracervical insemination (ICI), intra-uterine insemination (IUI), all three with or without ovarian stimulation (OS) and in vitro fertilisation (IVF), in couples with unexplained or male subfertility were contacted and invited to share their original data. In all datasets, we calculated the chances of natural conception for each couple with the validated prognostic Hunault model. We then constructed prognosis-by-treatment curves and tested whether the effect of prognosis on treatment outcome differed between the treatment strategies compared in the trials.

OUTLINE OF THE THESIS

The adherence to tailored expectant management (TEM) is evaluated in a large cohort study (n=1130) in **chapter 2.** In this chapter we also assess factors associated with non-adherence to TEM using multivariable logistic regression.

To make an inventory of patients' and professionals' barriers and facilitators of TEM we performed a qualitative study among both patients and professionals **(chapter 3)**. Semi-structured in-depth interviews were performed in 21 subfertile couples counseled for TEM and in 21 professionals.

In a nationwide survey, we assess the prevalence of those barriers and facilitators of TEM among 96 subfertile couples and 117 professionals. Multivariate analysis was performed to evaluate which factors predicted patients' appreciation of TEM and professionals' adherence to TEM **(chapter 4).**

The contents of chapters 2, 3 and 4 are used to develop an implementation strategy to implement TEM. In **chapter 5** a study protocol of a cluster randomized trial in which the (cost-) effectiveness of this implementation strategy can be tested, is described.

In most countries, there are limitations in public health funding for ART because of costs. Different countries have different ways to select subfertile couples for fertility treatment, not all evidence-based. To emphasize the importance of evidence based treatment selection for subfertile couples, we compared a selection strategy based on prognosis with a funding based selection strategy used in New Zealand **(chapter 6)**.

In **chapters 7 and 8** we evaluate if the chances of natural conception calculated with a validated prognostic model, could help in selecting the best treatment (IUI with or without OS, IVF) for couples with unexplained or mild male subfertility. We collected data of published RCTs comparing IUI with or without OS, IVF or EM in couples with unexplained or male subfertility and calculated their prognosis of natural conception. Subsequently, we analyse if this calculated prognosis could help to select the most effective treatment strategy for the individual couple.

Finally in the general discussion, the results presented in the abovementioned chapters are evaluated. The future implications for clinical practice and research are discussed **(chapter 9).**

In **chapter 10** we summarize the results of the studies presented in this thesis in both English and Dutch.

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PART I

Implementation of tailored expectant management

CHAPTER 2

Tailored expectant management, risk factors for non-adherence

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ABSTRACT

Introduction

prediction models for spontaneous pregnancy are useful tools to prevent overtreatment, complications and costs in subfertile couples with a good prognosis. The use of such models and subsequent expectant management in couples with a good prognosis are recommended in the Dutch fertility guidelines, but not fully implemented. In this study, we asses risk factors for non-adherence to tailored expectant management.

Methods

Couples with mild male, unexplained and cervical subfertility were included in this multicenter prospective cohort study. If the probability of spontaneous pregnancy within 12 months was ≥40%, expectant management for 6 to 12 months was advised. Multivariable logistic regression was used to identify patient and clinical characteristics associated with non-adherence to tailored expectant management.

Results

we included 3,021 couples of whom 1,130 (38%) had a ≥40% probability of a spontaneous pregnancy. Follow-up was available for 1,020 (90%) couples of whom 214 (21%) had started treatment between 6 and 12 months and 153 (15%) within 6 months. A higher female age and a longer duration of subfertility were associated with treatment within 6 months (OR 1.06; 95% CI 1.01 to 1.1, OR 1.4; 95% CI 1.1 to 1.8).A fertility doctor in a clinical team reduced the risk of treatment within 6 months (OR 0.62; 95% CI 0.39 to 0.99).

Conclusion

in couples with a favorable prognosis for spontaneous pregnancy, there is considerable overtreatment, especially if the woman is older and duration of the subfertility is longer. The presence of a fertility doctor in a clinic may prevent early treatment.

INTRODUCTION

In 50% of subfertile couples no major cause of the unfulfilled child wish is found (Aboulghar M et al. 2009). In these couples, the chances of a spontaneous pregnancy can be calculated with validated prediction models (Hunault et al. 2004; van der Steeg et al. 2007a). If chances on spontaneous pregnancy are 30% or higher, treatment offers no genuine benefit and expectant management is preferable (Steures et al. 2006). Tailored expectant management - expectant management for 6 to 12 months in couples with a good prognosis - prevents unnecessary early treatment and its complications, such as multiple pregnancies, and costs. For this reason tailored expectant management is recommended in the Dutch Fertility Guidelines.

Nevertheless, the use of prognostic models and subsequent expectant management is not fully applied in clinical practice. In a study on the quality of Dutch fertility care, the initial fertility assessment resulted in only 23% of the cases in both a diagnosis and a prognosis (Mourad et al. 2008). On the other hand, the number of ART cycles performed in Europe has more than doubled in the period 1997-2006 (de Mouzon et al. 2010). Implementation of prognostic models and subsequent tailored expectant management may slow down this increase without reducing pregnancy rates.

A better understanding of the factors associated with non-adherence may prevent early treatment and can improve the implementation of tailored expectant management. The aim of this study was to identify patient and clinical characteristics associated with an early start of fertility treatment in couples with a good prognosis.

Material and Methods

Between January 2002 and February 2004, 5,214 consecutive couples presenting at 38 hospitals in The Netherlands were invited to participate in a prospective cohort study. The Institutional Review Board of the Academic Medical Centre in Amsterdam approved the protocol. The board of directors of all participating hospitals gave local approval to the study. The study protocol was discussed with the gynaecologists of all participating hospitals, after which they agreed to participate. All couples underwent a basic fertility work-up according to the guidelines of the Dutch Society of Obstetrics and Gynecology. The details of this work-up have been described in detail previously (van der Steeg et al. 2007b).

Couples with bilateral tubal pathology, severe male factor, or anovulation were excluded from this study. The probability of a spontaneous pregnancy was calculated using the prognostic model of Hunault (Hunault et al. 2004; www.amc.nl/prognosticmodel 2010). Couples with a probability of natural conception $<40\%$ were invited to participate in various randomised controlled trials, depending on their diagnosis (Steures et al. 2006; Steures et al. 2007a; Steures et al. 2007b) or were counseled for treatment according to the Dutch fertility guidelines. Couples with a probability of natural conception of 40% or higher were recommended tailored expectant management for 6 to 12 months. Physicians were free to

start treatment at any time. Follow-up started at the completion of the fertility work-up and ended after 12 months. Primary outcomes were patient and clinical characteristics associated with non-adherence to tailored expectant management.
Including data of 1000 couples in the logistic regression analysis, and analyzing a binary feature, we would have 80% power at a 0.05 significance level to detect odds ratios for non-adherence of 1.4 or higher, assuming a 50% prevalence and a baseline probability of 0.36. At a 20% prevalence, statistically significant odds ratios of 1.6 or higher could be detected (Hsieh et al. 1998)

Analysis

In this analysis, we included couples with a calculated probability of natural conception of 40% or higher. We focused on patient and clinical characteristics associated with non-adherence to tailored expectant management. Non-adherence was defined as treatment within 6 months of couples with calculated probability of natural conception of 40% or higher.
A Kaplan-Meier curve was plotted to illustrate the cumulative fraction of couples with a good prognosis who started treatment over time. Multivariable logistic regression was used to identify patient and clinical characteristics that were associated with non-adherence to expectant management in patients with a good prognosis. Associations between patient and clinical characteristics and non-adherence were expressed as odds ratios and corresponding 95% confidence intervals.
We evaluated the patient characteristics female age, duration of subfertility, previous live birth or miscarriage, and socio-economic status. Socio-economic status was obtained from the Dutch Institute for Social Research/SCP based on the mean income level in a postal code area, the percentages inhabitants without a paid job and the percentage of inhabitants with a low education level. In addition, we evaluated a number of characteristics of the clinic: presence of a dedicated fertility doctor, presence of a regular fertility meeting, clinic with an IVF-ICSI lab or a satellite clinic (satellite clinics can initiate and monitor the stimulation phase and refer to another hospital for both oocyte retrieval and embryo transfer). A fertility meeting is weekly or monthly meeting with the staff-members were fertility patients are discussed.
Missing data were imputed using 'aRegImpute' imputation function on Splus 6.0. This is an efficient implementation of Bayesian multiple imputation, a recommended state of the art method (Schafer and Graham 2002). More details of this procedure described in detail elsewhere (van der Steeg et al. 2006). For the analysis we used SPSS 16.0. (Statistical Package for the Social Sciences: SPSS, Chicago, IL, USA).

Results

During the study-period we registered 5,214 subfertile couples, of whom 3,021 couples had normal semen quality, at least one patent tube and an ovulatory cycle. Of these couples, 1,130 (37%) had a probability of 40% or higher (figure 1). In this group, 110 couples were lost to follow-up (10%) and not used in further analyses.

Imputation was done on all patients who had at most two missing values in the six core prognosticators for spontaneous pregnancy, which was the case 4.3% of all data points. Of the 1,020 couples in our analyses, 367 (36%) couples started treatment within 12 months:

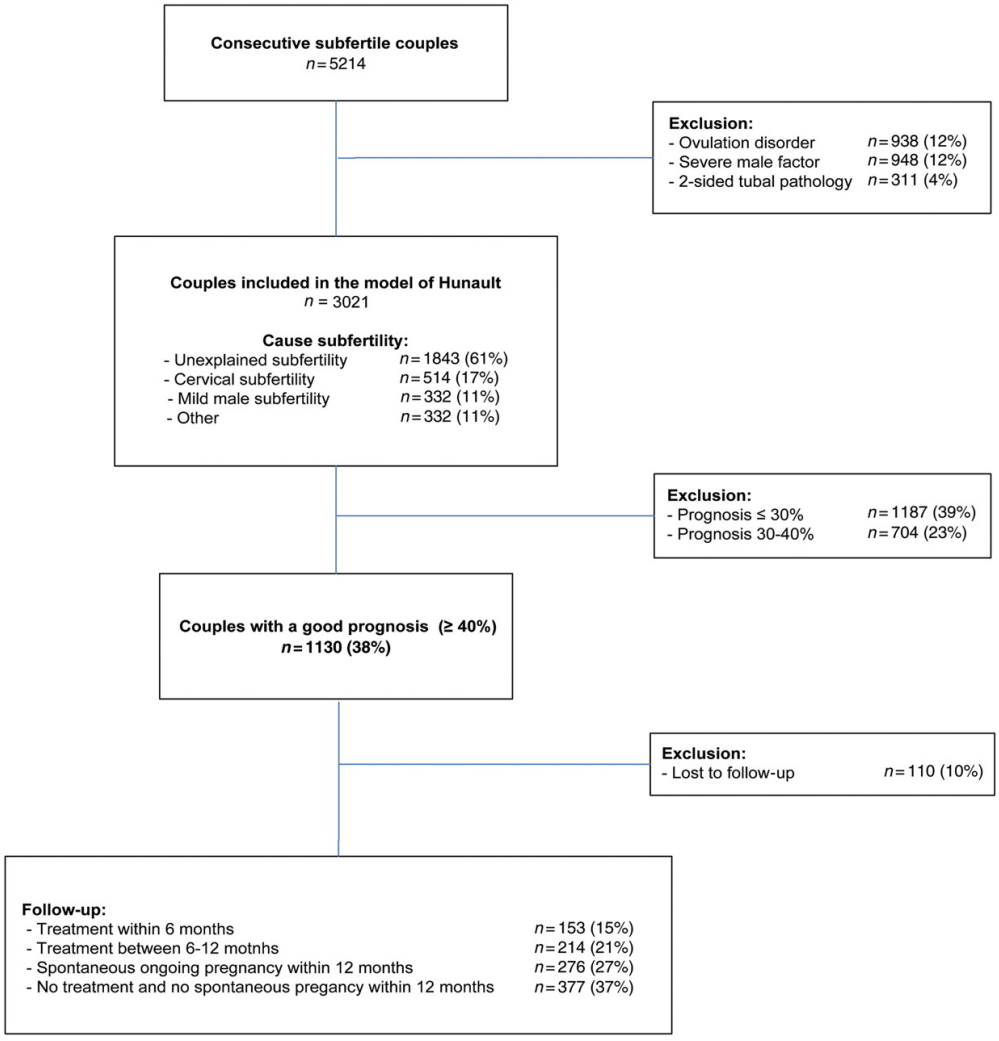

Figure 1. Study Profile

153 (15%) did so within 6 months and 214 (21%) between 6 and 12 months. Follow up ended when treatment was started. Forty-two percent of the couples that did not start treatment, had a spontaneous ongoing pregnancy within 12 months (276 couples, 27% of all couples) and 377 couples (58% of the couples that did not start treatment, 37% of all couples) had no spontaneous ongoing pregnancy and did not start treatment within 12 months. The Kaplan-Meier curves in Figure 2 show the fraction of couples who started treatment and the fraction with an ongoing pregnancy as a function of time after the fertility work-up.

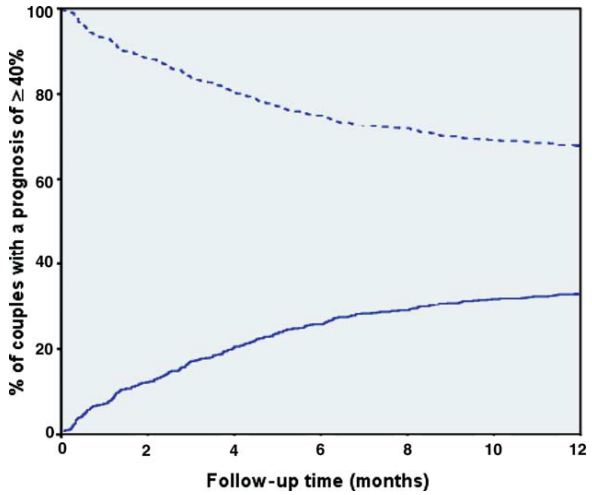

Figure 2. A Kaplan-Meier Curve of the fraction of couples who started treatment over time in relation to the fraction of couples without a spontaneous ongoing pregnancy. Dashed line represents the fraction of couples without a spontaneous ongoing pregnancy. Continuous line represents the fraction of couples who started with treatment.

Characteristics of patients and clinics of the following four groups are summarized in Table 1: couples who started treatment within 6 months, couples who started treatment between 6 and 12 months, the couples with a spontaneous ongoing pregnancy within 12 months and the couples without treatment and without an ongoing pregnancy within 12 months.

Table 1. Baseline-characteristics of the 1,020 couples with a prognosis ≥40%

	Treatment within 6 months n=153 (15%)	Treatment between 6-12 months n=214 (21%)	Spontaneous ongoing pregnancy within 12 months n=276 (27%)	No Treatment & no spontaneous ongoing pregnancy within 12 months n=377 (37%)
PATIENT CHARACTERISTICS				
Mean maternal age in years (SD)	31.9 (4.4)	31.2 (3.8)	31.1 (3.7)	30.8 (3.84)
Mean duration of subfertility in years (SD)	1.69 (0.77)	1.64 (0.62)	1.49 (0.71)	1.65 (0.70)
History ≥1 live birth with or without miscarriages (%)	48 (32%)	62 (29%)	92 (34%)	107 (28%)
History ≥1 miscarriage (%)	27 (18%)	21 (10%)	48 (19%)	42 (11%)
Socio Economic Status (%)				
High	23 (15%)	40 (18%)	47 (17%)	65 (17%)
Median	129 (70%)	141 (67%)	182 (66%)	243 (65%)
Low	23 (15%)	33 (15%)	47 (17%)	69 (18%)
CHARACTERISTICS of the CLINIC				
Fertility meeting (%)	78 (52%)	140 (65%)	168 (62%)	244 (64%)
Fertility doctor (%)	76 (51%)	148 (68%)	162 (60%)	244 (64%)
Clinic with IVF-ICSI license, (%)	21 (14%)	36 (17%)	47 (17%)	80 (21%)
Clinic with Satellite IVF (%)	89 (60%)	116 (55%)	133 (49%)	152 (40%)

The results of the multivariable logistic regression analysis of non-adherence to tailored expectant management, using patient and clinic characteristics, are summarized in Table 2. A higher female age and a longer duration of subfertility were each associated with treatment within 6 months (OR 1.06; 95% CI 1.01 to 1.1 and OR 1.4; 95% CI 1.1 to 1.8, respectively). A history of at least one live birth was not associated with early treatment. Couples with a history at least one miscarriage were more often treated within 6 months than couples without, but this difference did not reach statistical significance (OR: 1.54; 95% CI 0.93 to 2.6). Socioeconomic status and a regular fertility meeting were not associated with treatment within 6 months. The presence of a dedicated fertility doctor in a clinical team reduced the chance of starting treatment within 6 months (OR 0.62; 95% CI 0.39 to 0.99). The presence of an IVF-ICSI lab was not associated with early treatment, but we observed more frequent

early treatment in satellite clinics (OR 1.43; 95% CI 0.89 to 2.3), but this difference was not significant.

Table 2. Factors associated with treatment within 6 months in couples with a good prognosis, logistic regression

	Treatment within 6 months n=153 (15%)	
PATIENT CHARACTERISTICS	OR	95% CI
Mean maternal age (per year older)	1.06	1.01 to 1.1
Mean duration of subfertility (per year longer)	1.37	1.1 to 1.8
History ≥1 live birth with or without miscarriages (%)	0.99	0.65 to 1.5
History ≥1 miscarriage (%)	1.54	0.93 to 2.6
Socio Economic Status (%)		
High	0.88	0.53 to 1.5
Low	0.99	0.59 to 1.6
CLINICAL CHARACTERISTICS		
Fertility meeting (yes)	0.84	0.52 to 1.36
Fertility doctor (yes)	0.62	0.39 to 0.99
Clinic with IVF-ICSI license (yes)	0.89	0.47 to 1.7
Clinic with Satellite IVF (yes)	1.43	0.89 to 2.3

DISCUSSION

In this study we found that in one out of three couples with a good prognosis for spontaneous pregnancy, treatment was started within 12 months, and in one out of seven even within 6 months. Higher female age and a longer duration of subfertility were significantly associated with treatment within 6 months. The presence of a dedicated fertility doctor in a clinical team reduced the risk of early treatment within 6 months.

It is remarkable that female age and duration of subfertility were risk factors for early treatment in couples with a good prognosis because they are already main prognostic factors in the model of Hunault. So the clinician accounts for these factors when calculating the prognosis and when the prognosis is good the clinician uses the same factors again to refrain from expectant management. We hypothesize that this clinically important paradox transpires from other patients and physician-related factors. Physicians describe a lack of

confidence in their ability to convince patients about low success rates of intra-uterine insemination and the risk of multiple pregnancies (Haagen et al. 2005). In subfertile couples, there is a high sense of urgency leading to pressure for treatment, which can increase with age and duration of subfertility. In couples with unexplained miscarriages for whom no effective treatment is available, there is an instinctive drive to 'do something' from both patients and doctors (Rai and Regan 2006; Kaandorp et al. 2010).

A strength of this study is the large number of couples included in the cohort, which was prospectively assembled in a multicentre setting. A potential weakness of this study is that we measured the adherence to a study protocol instead of the adherence to an (inter)national guideline. As the recruiting doctors in this cohort will be more dedicated compared to an 'average doctor', we hypothesize that early treatment in daily practice must be even higher, as has been demonstrated previously (Mourad et al. 2008).

In our study 36% of the couples had a good prognosis and were eligible for expectant management. This fraction is in concordance with a longitudinal cohort study, performed between 2002 and 2006 in the Netherlands. In this cohort of newly referred subfertile couples, 45% of the 1,391 couples were eligible for tailored expectant management (Brandes et al. 2010). In contrast, the contribution of IVF in couples with 'unexplained subfertility' and 'ovulation disorders' was extremely limited (ongoing pregnancy rates of 13 and 4.5%, respectively) compared to patients with 'tubal factor', 'endometriosis' and 'male factor' in whom pregnancy rates were 45, 45 and 37%, respectively. Steptoe and Edwards introduced IVF to bypass tubal blockage and apparently, IVF is still only effective for the indications for which it was invented, i.e. fertilisation failure due to the inability of the male and female gametes to meet or the inability of the spermatozoa to penetrate the egg.

Early treatment is a common phenomenon in fertility care. For example, the increasing use of preimplantation genetic screening (PGS) has been debated widely, even though there is no evidence of increased live births after PGS (Mastenbroek et al. 2008a; Mastenbroek et al. 2008b; Twisk et al. 2008). Apart from harm, costs and complications, early treatment is also to be avoided because of its negative impact on the patients' physical and psychological well being (Cousineau and Domar 2007; Kallen et al. 2005).

In conclusion, this study shows that advanced female age, longer duration of subfertility, a history of at least one miscarriage and work up in a satellite clinic were associated with early treatment in couples with a good prognosis. An increased awareness of these factors may help to prevent overtreatment, contributing to the development of a strategy to implement tailored expectant management. Before this implementation strategy can be developed, we recommend performing a qualitative study among patients and professionals to evaluate the barriers and facilitators of tailored expectant management.

Authors' roles

B.W.J.M., F.V. and P.G.A.H. designed the study. J.W.S. and P.S. co-ordinated the cohort study, collected the data and sought ethical approval. N.B did the analysis under the supervision of B.W.J.M., J.W.S., K.O. and P.M.M.B. provided statistical advice. N.B wrote the manuscript and all authors helped to prepare the final report.

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Chapter 3

Patients' and professionals' barriers and facilitators of tailored expectant management in subfertile couples with a good prognosis of a natural conception

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ABSTRACT

Background

European guidelines on fertility care emphasize that subfertile couples should receive information about their chances of a natural conception and should not be exposed to unnecessary treatments and risks. Prognostic models can help to estimate their chances and select couples with a good prognosis for tailored expectant management (TEM). Nevertheless, TEM is not always practiced. The aim of this study was to identify any barriers or facilitators for TEM among professionals and subfertile couples.

Methods

A qualitative study was performed with semi-structured in-depth interviews of 21 subfertile patients who were counselled for TEM and three focus-group interviews of 21 professionals in the field of reproductive medicine. Two theoretical models were used to guide the interviews and the analyses. The primary outcome was the set of identified barriers and facilitators which influence implementation of TEM.

Results

Among the subfertile couples, main barriers were a lack of confidence in natural conception, a perception that expectant management is a waste of time, inappropriate expectations prior to the first consultation, misunderstanding the reason for expectant management and overestimation of the success rates of treatment. Both couples and professionals saw the lack of patient information materials as a barrier. Among professionals, limited knowledge about prognostic models leading to a decision in favour of treatment was recognized as a main barrier. A main facilitator mentioned by the professionals was better management of patients' expectations.

Conclusions

We identified several barriers and facilitators which can be addressed to improve the implementation of TEM. These should be taken into account when designing future implementation strategies.

INTRODUCTION

Approximately 9% of all couples of reproductive age fail to conceive after 12 months of unprotected intercourse (Boivin et al. 2007; Gnoth et al. 2003). When they subsequently undergo a fertility work up, no major cause can be found in half of them (Aboulghar M et al. 2009). Previous studies have shown that many of these couples can still conceive without treatment (Brandes *et al.*, 2010;Collins, 2004;Evers *et al.*, 1998;Pinborg *et al.*, 2009;Steures *et al.*, 2006). It is therefore crucial to be aware of the prognosis in these couples so we can discriminate between those who would benefit from active treatment from those who are likely to conceive naturally (Brandes et al. 2011).

The chances of a spontaneous pregnancy can be calculated with the help of validated prediction models (Hunault et al. 2004; van der Steeg et al. 2007a). When the calculated prognosis to conceive within 12 months is ≥30%, tailored expectant management (TEM) is as effective as treatment, which makes TEM a cost effective strategy that prevents overtreatment, complications and costs (Steures et al. 2006). Therefore, expectant management is in the Dutch fertility guidelines recommended for couples with a ≥30% chance to conceive within 12 months (NVOG 2004). In agreement with this, both the European Society of Human Reproduction and Embryology (ESHRE) guidelines and the guidelines of the National Institute of Clinical Excellence (NICE) emphasize that couples should not be exposed to unnecessary risks or ineffective treatments and encourage that each couple should receive information about the estimate of their chances of natural conception (ESHRE 2001; NICE 2004).

Despite this, the number of Assisted Reproductive Therapy (ART) cycles performed in Europe has more than doubled in the period 1996 to 2006 (Andersen et al. 2009). This development is disconcerting for several reasons. First, this increase is likely to lead to a high number of multiple pregnancies. Even though multiple pregnancy rates per ART cycle are decreasing, the risks are still substantially higher than those in spontaneous conceptions. Multiple pregnancies are associated with a higher morbidity and mortality in both mothers and neonates (Helmerhorst et al. 2004). Second, ART carries a significant physical and a psychological burden (Verberg *et al.*, 2008;Verhaak *et al.*, 2002;Verhaak *et al.*, 2007). Third, ART is expensive and puts considerable financial strain on societies where ART is reimbursed or on the couples in societies where ART is not or only partially reimbursed.

For all these reasons, it is important to treat couples who genuinely need ART and are likely to benefit from it. Prognostic models, such as the prognostic model of Hunault, can help to select those couples. Nevertheless, these models and subsequent TEM are not fully applied in clinical practice (Mourad *et al.*, 2008;van den Boogaard *et al.*, 2011). A clear understanding of why the prognostic models and subsequent tailored expectant management are not used in practice is lacking. Therefore, the aim of this study was to identify patients' and professionals' barriers and facilitators for the implementation of TEM.

Materials and Methods

A qualitative study was performed with subfertile couples and professionals working within the field of reproductive medicine. We performed semi structured in depth interviews among subfertile couples and professionals in an individual and group-setting, respectively. We opted for semi-structured interviews to let the participants (i.e. patients and professionals) talk freely with structured guidance from the interviewer, using a topic list. The topic list (appendix 1) was based on the literature and knowledge and experiences of experts in the fields of reproductive medicine, qualitative research or implementation research, all co-authors of this article. The topic list was adapted when new barriers or facilitators were identified. Prior to the start of the interviews, confidentiality was assured and the process of the interview was explained. We continued interviewing until data saturation was achieved, i.e. no additional information was gathered during subsequent interviews. The interviews were audio taped and fully transcribed and quotes were all made anonymous. The primary outcome was the set of identified barriers and facilitators which might influence the implementation of TEM.

The subfertile couples whom we interviewed were diagnosed with unexplained subfertility and had a chance to conceive within 12 months of ≥30%. For that reason they had been counselled for TEM. We interviewed couples that had been advised TEM between April 2008 and April 2009. The couples were recruited from two hospitals in Amsterdam: one academic hospital and one non-academic teaching hospital. We chose for an individual setting while we expected in this setting patients would feel more freely to speak. For the same reason we preferred to interview the woman men and women separately. We purposively sampled couples with different ethnic backgrounds and education levels because we hypothesized these characteristics could influence their experience of the expectant management. The couple could choose the location of the interview which was conducted either at their hospital or at their own home. We preferred to interview the man and the woman separately, unless the couple preferred to be interviewed together. We performed 15 interviews with 21 patients. Six women and three men were interviewed individually and six couples were interviewed together. The interviews were performed by two researchers (N.B. and A.B.) and took 30-50 minutes.

We also interviewed 21 professionals in 3 focus-group interviews. Gynaecologist specialized in Reproductive Medicine and registered as such at the Dutch Society of Obstetrics and Gynaecology (NVOG) and gynaecologists with interest in the field of reproductive endocrinology and infertility and fertility doctors, from 17 different hospitals from 4 different regions were all invited per mail. In total we invited 53 professionals: 3 gynaecologists and 7 fertility doctors from an academic hospital, 27 gynaecologists and 16 fertility doctors from non academic hospitals. Gynaecologists and fertility doctors of 10 different academic and non academic hospitals from 4 different provinces in the Netherlands participated voluntary. In the Netherlands fertility doctors are basic doctors working in the fertility care, while most gynaecologists also work in the field of obstetrics and general gynaecology. Prior to

the interviews, it was unclear to what extent the professionals used the prognostic models and subsequent TEM. The group setting was chosen because we expected that the group interaction might lead to the identification of more relevant barriers. The focus-group interviews were guided by a chairman (E.B.) and another researcher (N.B.) attended as a back up. The focus- group interviews took 60-90 minutes.

Setting

In the Netherlands intra uterine insemination (IUI) is performed in 91 of the country's 101 hospitals and IVF is performed in 13 licensed hospitals. All 101 hospitals can perform a fertility work up and advice on TEM. The costs of IUI (for an undefined number of cycles) and the first three fresh In Vitro Fertilisation (IVF) or Intra Cytoplasmatic Sperm Injection ICSI cycles are currently reimbursed by medical insurance companies. In the Netherlands it is compulsory to have a medical insurance. Professionals have access to prognostic models via 2 websites (www.amc.nl/prognosticmodel and www.freya.nl), with the help of electronic patient files or with the use of paper versions of the models.

Analysis

All interview transcripts were independently analysed by two researchers: the interviews with the subfertile couples by A.B. and N.B. and the focus-group interviews with the professionals by E.B. and N.B. MAXqda10, an analysis program for qualitative data-analysis, was used for the analysis which was based on the strategy described by Boeije et al. (Boeije 2010). The aim of the analysis was to conceptualize the content of the interviews in structured categories. First, the interviews were analysed by means of line by line coding, using a constant comparison method: newly gathered data are continually compared with previously collected data and their coding in order to refine the development of theoretical categories. After this open coding, the codes were rearranged by axial coding and finally categorised by means of selective coding. Axial coding is relating codes to each other and selective coding is the process of choosing one category to be the core category, and relating all other categories to that category. Finally, all transcripts were reread and recoded, using the improved coding structure to ensure no codes were missing. To ensure consistency, codes were compared and any discrepancies were resolved by discussion between the two researchers. Differences of opinions were discussed with a third researcher (MZ for the patient interviews and WN for the focus-group interviews).
We used two theoretical models to group our findings within four domains: characteristics of the intervention itself (TEM), of the professional, of the patient and of the context (Cabana et al. 1999; Peters et al. 2003).

Results

Patient characteristics, summarized in Table I show a degree of variety in terms of educational and cultural backgrounds. Characteristics of the professionals are listed in Table II which shows the variation in experience and use of the prognostic model between gynaecologists (50%) and fertility doctors (100%).
Factors (barriers and facilitators) mentioned by at least two participants are listed in Table III (subfertile couples) and Table IV (professionals). Factors mentioned by more than 50% of the participants are described in the text and marked in the tables with an asterisk (*).In both the tables and the text, the barriers and facilitators are ranked by the frequency in which they are mentioned. Quotes illustrating some of the barriers and facilitators are provided in Appendix 2, Table 1.

Barriers and facilitators related to the implementation of TEM according to subfertile couples

There were 16 barriers and facilitators were identified among the 15 subfertile couples, i.e. 21 patients (Table III). Three men did not participate because they had no time or did not remember the details and referred us to their partners, who were more involved. Overall women were more committed and informed about the whole procedure than men. At the time of the interview, two couples were pregnant and three couples had started treatment of intrauterine insemination with controlled ovarian hyperstimulation. The other nine interviewed couples were still in the period of expectant management.

Domain 1, characteristics of the intervention
A lack of confidence in natural conception and a perception that expectant management is a waste of time were barriers in this domain. These two factors had a common underlying cause in that they were based on the perception of the couples that they had already been trying to conceive for a long period.
The subfertile couples could not remember the information that had been given concerning their prognosis and the reason for expectant management. Therefore, information provision by means of a brochure or a website about the prognostic model and subsequent expectant management was mentioned as a facilitator.
Domain 2, characteristics of the professional
Not informing the couple about the option of TEM during the first consultation was mentioned as a barrier in this domain. Couples expected treatment after the fertility work up unless they were already told beforehand that TEM was an option.

Domain 3, characteristics of the patient
Barriers mentioned in domain 3 were: inappropriate expectations prior to the first consultation, misunderstanding the reason for TEM, overestimation of success rates of

treatment, inability to comprehend and retain the information given during the consult and irrational interpretations of pregnancy chances. The last i.e. 'Irrational interpretations of chances' refers to the finding that despite awareness of their prognosis and understanding why it was better to wait, couples still wanted treatment. Couples saw treatment as a forgone conclusion after the fertility work up, did not understand why expectant management was advised and had unrealistic high expectations of treatment outcomes.

Domain 4, characteristics of the context
The length of time taken for the whole process was mentioned as a barrier: the period prior to the couples' hospital visit plus the subsequent time needed for the fertility work-up already took 'too long' such that tailored expectant management was seen as another delaying factor.

Barriers and facilitators related to the implementation of TEM according to professionals

Among the 21 professionals, 20 barriers and facilitators influencing the implementation of TEM were identified (Table IV). There was a wide range of knowledge and attitudes concerning prognostic models and subsequent TEM. For some professionals it made sense to use a prognostic model to plan TEM, but others had less faith in the TEM strategy and did not use it in their clinic on a regular basis.

Domain 1, characteristics of the intervention
Two barriers were identified in this domain: existing prognostic models do not include all the relevant predictors and a lack of appropriate patient information materials. The missing predictors within prognostic models mentioned by professionals were mainly lifestyle factors such as body mass index and frequency of coitus. To overcome the barrier 'lack of adequate patient information materials' the professionals suggested the development of a brochure and/or the introduction of a website.

Domain 2, characteristics of the professional
Limited knowledge about the prognostic models and subsequent TEM, - difficulties in convincing the couple who have their minds made up and - difficulties in counselling and communicating pregnancy chances, were barriers in the second domain. There was consensus that good counselling skills were very important to be able to communicate to the patient that TEM was their best treatment option at that moment.

A facilitator in this domain was the comparison between the spontaneous chances of a pregnancy with the realistic pregnancy chances after treatment. Professionals mentioned that many couples have unrealistically high expectations of treatment, which make it

difficult for the professional to convince them that TEM is the best option. In this way, the comparison helped in counselling the couples for TEM.

Domain 3, characteristics of the patient

The couples' high expectations of treatment, - urgency for action, - expecting immediate treatment after the fertility work up and the couples' misreading of chances were barriers in this domain. According to professionals, couples had too high expectations of treatment and the couples' urgency for action made it difficult to counsel them for TEM. Managing couples' expectations regarding treatment success and moment of treatment were mentioned as a major facilitator.

Domain 4, characteristics of the context

A regular fertility meeting involving other professionals, a clinical protocol based on local consensus, and centralisation of fertility care were facilitators mentioned in this domain. A fertility meeting is a weekly or monthly meeting, during which all fertility patients who have finished their basic fertility workup are discussed.

Table I. Patient characteristics

* Primary school or less, ** High school, *** University/post graduate

**** The place of birth of the patient or both parents is outside the Netherlands, excluding its dominions.

Characteristics	Value n (%)
Gender	
- Female	12 (57%)
- Male	9 (43%)
Age (median)	
Female (range)	32 (21-37)
Male (range)	35 (27-43)
Diagnosis	
Unexplained primary subfertility	9 (43%)
Unexplained secondary subfertility	12 (57%)
Prognosis (median, range)	36% (33% - 57%)
Duration subfertility (months) (median, range)	22 (18-48)
Education level	
Low*	4 (19%)
Medium**	6 (29%)
High***	11 (52%)
Ethnic background	
Dutch	12 (57%)
Non Dutch****	9 (43%)
- Turkish	2
- Moroccan	3
- Afghan	1
- Colombian	2
- Unknown	1

Table II. Characteristics of professionals

	Gynaecologists N = 9	**Fertility doctors N = 13**
Male, n (%)	3 (33%)	3 (23%)
Female, n (%)	6 (67%)	10 (77%)
Median age, (range)	48 (41-64)	34 (27-45)
Median years of expertise (range)	17 (8-35)	6 (1-13)
Academic hospital n(%)	1 (11)	5 (38)
Regular use of the prognostic model n (%)	4 (50)	13(100)

Table III. Barriers (b) and facilitators (f) of tailored expectant management (TEM) according the subfertile couples

* Factors mentioned by more than 50% of the participants

Domain 1 Characteristics of the intervention	*Domain 2 Characteristics of the professional*	*Domain 3 Characteristics of the patient*	*Domain 4 Characteristics of the context*
Lack of confidence in the natural conception (b) *	Not informing the couple about the option of TEM during the first consultation (b) *	Inappropriate expectations prior to the first consult (b) *	The length of time taken for the whole process (b) *
Patient information material about prognosis and TEM (f) *	Unclear way of counselling and communicating chances (b)	Misunderstandings the reason for TEM (b) *	Practice in other clinics (b)
A perception that TEM is considered as a waste of time (b) *	Not explicitly mentioning TEM, but conceal TEM in waiting period for treatment (f)	Overestimation of the success rates of treatment (b) *	
Complexity of the prognostic model (b)		Inability to comprehend and retain information given during the consult (b) *	
		Irrational interpretation of pregnancy chances (b) *	
		Progressing female age (b)	
		Twin is a welcome complication (b)	

Table IV. Barriers (b) and facilitators (f) of tailored expectant management according professionals
* Factors mentioned by more than 50% of the participants

Domain 1 Characteristics of the intervention	*Domain 2 Characteristics of the professional*	*Domain 3 Characteristics of the patient*	*Domain 4 Characteristics of the context*
Existing prognostic models do not include all the relevant predictors (b) *	Limited knowledge about the prognostic models and subsequent TEM (b) *	High expectations of success with treatment (b) *	A regular Fertility meeting (f) *
Lack of adequate patient information materials (b) *	Difficulties convincing couples who have their minds made up (b) *	Urgency for action in the couple (b) *	Local protocol (f) *
Not convinced about the usefulness of the prognostic models and TEM (b)	Difficulties in counselling and communicating chances (b) *	Expectations of immediate treatment after the fertility work up (b)*	Local consensus (f) *
Explaining TEM takes time (b)	Comparison of treatment chances versus spontaneous pregnancy chances (f) *	Couples' misinterpretation of chances (b) *	Centralisation of fertility care (f) *
	Close relationship with couple (b)	Progressing female age (b)	Regional organisation (f)
		Miscarriage population (b)	

DISCUSSION

We identified a wide variety of barriers and facilitators influencing the implementation of tailored expectant management for unexplained subfertility. Among the subfertile couples the main barriers were: I) lack of confidence in natural conception, II) inappropriate expectations at the first consultation, III) misunderstanding the reason for the expectant management, and IV) overestimation of the chances of success with treatment. Both couples and professionals experienced the lack of patient information materials as a barrier. Among the professionals limited knowledge about prognostic models and subsequent tailored expectant management and inappropriate expectations of couples were recognised as main barriers. Better management of couples' expectations was suggested as a main facilitator.

Many barriers involved patients, which is in line with results of existing studies on barriers for implementation within the scope of fertility health care (Haagen et al. 2005; van Peperstraten et al. 2008b). The professional' barriers concerning the difficulties counselling, convincing and communicating with the couple can be summarised as a lack of self-efficacy, which is a common barrier in guideline adherence (Cabana et al. 1999; Haagen et al. 2005; Lugtenberg et al. 2009). The barriers concerning misunderstanding of prognosis, inappropriate expectations and lack of patient information materials all have to do with communication and information provision. Previous research among 1,499 Dutch subfertile couples who fulfilled a questionnaire concerning their experiences with fertility care also found that information provision is poor and in need for improvement (Mourad et al. 2009; Mourad et al. 2010). Also in other countries, couples often express a need for more written information about fertility treatment (Schmidt 1998; Souter et al. 1998). The subfertile couples' preference for treatment compared to expectant management is consistent with the findings of several other studies, including a three arm randomised controlled trial in which women treated actively with intra uterine insemination or clomifene citrate, found the process of treatment more acceptable than those randomised to expectant management (Bhattacharya et al. 2008). In a questionnaire study where coping strategies of couples presenting for IVF were evaluated, taking direct action was the coping strategy most frequently used (Edelmann et al. 1994). A preference study evaluating patients' preference between intra uterine insemination with or without controlled ovarian hyperstimulation and expectant management, couples preferred treatment when the treatment independent pregnancy chances in the next 12 months were lower than 50% and 40%, respectively (Steures et al. 2005).

Only half of the gynaecologists, but all of the fertility doctors interviewed in this study reported using a prognostic model to recommend subsequent tailored expectant management on a regular basis. This corresponds with a previous study about risk factors for overtreatment, in which the non-adherence to TEM was 40% and the presence of a fertility doctor was associated with an increase of this adherence (van den Boogaard et al. 2010). This variation in adherence to TEM in the interviewed professionals as well as the heterogeneity of the cultural background and educational level of the interviewed patients leaded to the

identification of a wide variety of barriers and facilitators and is there for a stronghold of our study.

In our study, both the subfertile couples and the professionals mentioned difficulties in interpreting and communicating chances of success. From previous research we know that the perception of chances is influenced by the way chances are framed. In this respect a comparison with a baseline-risk and the use of visual tools can help to communicate chances in a more user friendly manner. (Edwards and Prior 1997; Grimes and Snively 1999; Shiloh S and Saxe L 1989; Wertz et al. 1986). Regarding the chances on a natural conception in our study, no defined 'baseline prognosis' is available yet and the professionals in this study did not use visual tools to facilitate the communication of the prognosis. So, here is an opportunity for improvement.

Among the subfertile couples, women were generally more committed and informed than men. This gender difference is in concordance with other studies where were couples asked about their expectations and motivation for seeking fertility treatment. In most cases the woman sought treatment for herself and her partner and the man more for his partner than for himself (Schmidt et al. 2003).

We realise there are some limitations in this study that should be considered. First, all interviewed couples were recruited from only two hospitals both in the region of Amsterdam. The barriers and facilitators could be biased by the way fertility care was provided in those two hospitals. However, the two hospitals are large training hospitals, one academic and one non academic hospital, working according the guidelines and we do not expect the provided fertility care differs much from other hospitals. Couples living in rural areas might have a different view on tailored expectant management compared to patients from an urban area. Nevertheless we think patients' origin has limited influence on the experienced barriers and facilitators because in such a densely inhabited country as the Netherlands differences between urbanised and non urbanised areas are small and with the current use of internet and social media, patients from the 'non urbanised' areas are able to be as informed and up to date as patients from the "non- urbanised areas". Moreover, further quantification of the barriers and facilitators is needed among patients from more hospitals. Second, a limitation of this study might be the Dutch setting. Dutch patients and professionals may have different opinions about the use of prognostic models and subsequent tailored expectant management than patients and professionals in other countries. However, the barriers and facilitators we found were not specifically related to the Dutch setting. We therefore consider the identified barriers applicable for an international setting, if the reimbursement system is comparable. Third, the participation rate of the professionals (21 out of 54) was low, possibly because the participation was voluntarily. Because we continued interviewing until data saturation was achieved, we do not think this response influences the set of identified barriers and facilitators. Fourth, a potential limitation of qualitative research is the introduction of bias by different interpretations of the transcripts. Therefore, two individual researchers examined all transcripts and differences of opinions were discussed with a third researcher.

Discrepancies were discussed until agreement was reached. Finally, although we aimed to interview men and women separately, we interviewed half of the couples together at their request. Nevertheless, we did not find different results in couples interviewed together compared to couples interviewed separately. We also did not get the impression during the interviews that one of the interviewees was unable to speak freely because of the presence of the other partner.

As stated above, to measure the impact of the barriers and facilitators found in this study a further quantification of these results is needed. After quantification of these barriers and facilitators an implementation strategy can be developed. Based on the results of this study, this strategy needs to focus on better management of couples' expectations, education of the professionals about prognostic models and subsequent tailored expectant management, training professionals to communicate about tailored expectant management and offering adequate patient information materials.

In summary, this study gives insight into the barriers and facilitators of the use of prognostic models and subsequent tailored expectant management. Knowledge of these factors may help to improve implementation of tailored expectant management in clinical practice and reduce potentially harmful and costly overtreatment.

Ethical approval

Subjects did not undergo additional investigations nor treatment. As assessed by the Institutional Review Board (IRB) of the Academic Medical Centre Amsterdam, the study was not subject to the Dutch "Medical Research Involving Human Subjects Act" (meaning that no formal IRB approval was needed).

Contributors

B.W.J.M., F.V. and P.G.A.H. initiated and designed this study and contributed in the interpretation of the data. N.B, E.B. and A.B. performed the interviews and did the analysis under the supervision of M.Z and W.N. S.B. contributed in the interpretation of the data. N.B wrote the manuscript and all authors helped to prepare the final manuscript.

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APPENDIX 1: TOPIC-LISTS

Focus group interviews with professionals

Current practice concerning prognostic model and expectant management
Professional opinion concerning prognostic model and expectant management
Experienced barriers concerning the prognostic model and expectant management:
- No knowledge about the model
- Model not available
- No consensus with the model or subsequent expectant management
- Difficult to counsel the couple, while the couple wants treatment
- Treatment means more income

Possibilities to stimulate the prognostic model and tailored expectant management:
- Fertility meeting
- Protocol with the prognostic model
- Local consensus
- Electronic patient file with application concerning prognostic model

Topic-list interviews with subfertile couples

Expectations before the first consult: fertility work up & treatment
First consult:
- Change of expectations
- Option expectant management discussed?

Influence of the environment:
- Couples with children
- Emotional support

First reaction on expectant management:
- Rational and emotional
- Faith in spontaneous conception
- (Dis)advantages treatment; OHSS, Multiple pregnancy, Physical and psychological burden
- Need for more information?
- Need for more coaching/support in the expectant management period.

APPENDIX 2, TABLE 1: QUOTES ILLUSTRATING THE IDENTIFIED BARRIERS AND FACILITATORS

	Barrier/facilitator	Quote
PATIENTS		
Domain 1: Characteristics of the intervention	Lack of confidence in the natural conception	*"At that moment, that they sent us home to try it again ourselves I really thought: but we are already trying for such a long time, why would we succeed now? We did not come to the hospital to be sent home!"*
Domain 2: Characteristics of the professional	Not informing the couple about the option of TEM during the first consultation	*"If we would have known from the beginning that expectant management could be an option I could have changed my expectations and I would not have been so disappointed and sad."*
Domain 4: Characteristics of the context	The length of time taken for the whole process	*"When you add up the time between all the investigations and the waiting time….it is really time for action now."*
PROFESSIONALS		
Domain 1: Characteristics of the intervention	Existing prognostic models do not include all the relevant predictors	*"When I see a coitus frequency of once a month and a lifestyle of which I think hallelujah, then I assume the model can be improved on those items"*
Domain 2: Characteristics of the professional	Difficulties in counselling and communicating chances	*"I think it is unbelievably difficult to start no treatment after the fertility work up: the patients have the strong feeling they have already been trying for such a long time and they come to you to hear a concrete proposal and then you have to tell you are going to do nothing? For me, that makes it really hard…"*
Domain 2: Characteristics of the professional	Comparison of treatment chances versus spontaneous pregnancy chances	*"When you are able to put the treatment chances in perspective of the chances spontaneously, it would be easier to counsel couples for expectant management…"*
Domain 3: Characteristics of the patient	Expectations of immediate treatment after the fertility work up	*"If you take your time for the first consultation and explain the steps of the fertility work up and all the options after the work up, including expectant management, you will save a lot of time, incomprehension, discussions and dissatisfied patients"*
Domain 4: Characteristics of the context	A regular Fertility meeting, a local protocol and local consensus	*"When I have to decide on my own this couple needs an expectant management I think the consult will end differently than when it was decided during a central fertility meeting. It feels more comfortable when it is discussed with the whole team"*

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Chapter 4

Tailored expectant management: a nationwide survey to quantify patients' and professionals' barriers and facilitators

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ABSTRACT

Background

prognostic models for natural conception help to identify subfertile couples with high chances of natural conception, who do not need fertility treatment yet. The use of such models and subsequent tailored expectant management (TEM) is not always practiced. Previous qualitative research has identified barriers and facilitators of TEM among patients and professionals. The aim of this study was to assess the prevalence of those barriers and facilitators and to evaluate which factors predict patients' appreciation of TEM and professionals' adherence to TEM.

Methods

we performed a nationwide survey. Based on the previously identified barriers and facilitators two questionnaires were developed and sent to 195 couples and 167 professionals. Multivariate analysis was performed to evaluate which factors predicted patients' appreciation of TEM and professional adherence to TEM.

Results

in total, 118 (61%) couples and 117 (70%) professionals responded and 96 couples and 117 professionals were included in the analysis. Patients' mean appreciation of TEM was 5.7, on a 10-point Likert scale. Patients with a lower appreciation of TEM had a higher need for patient information ($P = 0.047$). The professionals reported a mean adherence to TEM of 63%. Adherence to TEM was higher when professionals were fertility doctors ($P = 0.041$). Facilitators in the clinical domain were associated with a higher adherence to TEM ($P = 0.091$). Barriers in the professional domain had a negative impact on adherence to TEM ($P = 0.008$).

Conclusions

the limited implementation of TEM is caused by both patient and professional-related factors. This study provides practical tools to improve the implementation of TEM.

INTRODUCTION

In approximately 50% of subfertile couples, no major cause for their unfulfilled childwish is found (Brandes et al. 2011; The ESHRE Capri Workshop Group 2009; van der Steeg et al. 2007a). Almost half of those couples have moderate to high chances of natural conception and would benefit from expectant management (Brandes et al. 2010; Brandes et al. 2011; Collins et al. 1983; van der Steeg et al. 2007a). These couples can be identified by prognostic models (Hunault et al. 2004; Steures et al. 2006; van der Steeg et al. 2007a). The prognostic model of Hunault predicts the chance of natural conception within 12 months and contains the variables female age, duration of subfertility, primary or secondary subfertility, sperm motility and referral status and performed well in external validation in a cohort of more than 3000 couples (van der Steeg et al. 2007a). In a randomised controlled trial, expectant management for six months, in couples with an intermediate (30-40%) chance of natural conception, was as effective as treatment with intra uterine insemination (IUI) with ovarian stimulation (OS) (Steures et al. 2006). Based on these studies expectant management is recommended in our guidelines in couples with a chance of natural conception of ≥30% for at least 6 months (NVOG: national guideline subfertility 2011; NVOG guideline 2004). Nevertheless, the implementation of prognostic models and subsequent expectant management in couples with a good prognosis, i.e. tailored expectant management (TEM), is poor, leading to unnecessary treatment (van den Boogaard et al. 2011a).

Previous qualitative research has identified barriers and facilitators of TEM (van den Boogaard et al. 2011b). Among subfertile couples, the barriers are lack of confidence in the effectiveness of natural conception, expecting immediate treatment after the fertility work up, misunderstanding the reasons for expectant management and overestimating the success rates of treatment. Among professionals, limited knowledge and limited communication skills are experienced as the main barriers. Better management of patients' expectations is seen as one of the most important facilitators. Both professionals and patients indicate a lack of adequate patient information materials as a main barrier (van den Boogaard et al. 2011b). Knowledge of the impact of these barriers and facilitators on patients' appreciation of TEM and professionals' adherence to TEM is necessary to be able to implement TEM. Therefore, the aim of this study was to quantify the barriers and facilitators of TEM among patients and professionals in a nationwide survey and to analyse which factors influence patients' appreciation of TEM and professionals' adherence to TEM.

Materials and Methods

Study population

All subfertile couples who had been counselled for TEM for 6-12 months from seven hospitals (two academic and five non academic hospitals) from four different regions in the Netherlands were sent a questionnaire by post, 1-12 months after they had been counselled for TEM.

We included couples who were in their expectant management period of 6-12 months. These couples could as yet not have conceived, they could have conceived naturally in the TEM period or they could have started treatment in the TEM period. Couples who started treatment after their TEM period were excluded from the analysis because we suspected their appreciation might have been biased by their failure to become pregnant and needing treatment.
All Dutch gynaecologists sub-specialised in the field of reproductive medicine and registered as such with the Dutch Society of Obstetrics and Gynaecology (NVOG) were invited to participate. Next to that, all fertility doctors registered with the Dutch Society of Fertility Doctors (VVF) were invited. Fertility doctors are basic doctors who work in fertility care and had an in-house education in reproductive medicine. We invited the professionals to fill in an online questionnaire.

Setting

All 101 hospitals in the Netherlands do fertility work-ups and can advise tailored expectant management according to the national guideline (NVOG: national guideline subfertility 2011). In the Netherlands IUI with and without OS is performed in 91 hospitals. In Vitro Fertilisation (IVF) and Intra Cytoplasmatic Sperm Injection (ICSI) is performed in 13 licensed hospitals (Kremer et al. 2008b; Steures et al. 2007c)

Questionnaire

The questionnaires for the patients were sent by post between December 2010 and February 2011. The questionnaire included a letter, explaining the purpose of the study. To ensure the highest possible response rate we used a short questionnaire (maximum 15 minutes fill in time), prepaid return envelopes and two reminder questionnaires (Edwards et al. 2002). The two reminders were sent to non-respondents within a period of 10 weeks.
The link to the questionnaire for the professionals was sent by email in November 2010. The questionnaire itself was developed in surveymonkey.com and had also a maximum fill in time of 15 minutes. Two reminders were sent in a period of 10 weeks.

The questionnaires for both patients and professionals were based on previously identified barriers and facilitators for TEM (van den Boogaard et al. 2011b). The barriers and facilitators were translated into statements and with each statement, the participant could choose between *strongly disagree(1), disagree, neutral, agree and strongly agree(5)*. An example of a statement of a patients' barrier was: "I have no confidence in a good chance of natural conception" and the couple could report their level of agreement with this statement. An example of a statement testing a facilitator for professionals was: "I think that a regular fertility meeting would improve my adherence to TEM" and the professional could report their level of agreement.

Both questionnaires contained three parts. The questionnaire for the patients started with closed and open ended questions concerning baseline characteristics. The second part contained two closed-ended questions and five five-point-Likert scale items concerning expectations prior to the first consultation. The third part included interpretations of and experiences with TEM, divided into nine closed-ended questions and 27 five-point-Likert scale items. This last part also contained one question with a ten-point-Likert-scale concerning their appreciation of TEM. We defined appreciation of TEM as approval and understanding of TEM.

The questionnaires for the professionals' started with open and closed ended questions about the characteristics of the professional and the hospital. The second part consisted of four closed-ended questions, eight five-point-Likert scale items, and three open-ended questions concerning the use of the prognostic model and barriers for the use of the model. The third part contained seven closed-ended questions, 19 five-point-Likert scale items, and four open-ended questions about barriers and facilitators of advising expectant management. This last part also contained one question with a ten-point-Likert- scale about the professionals' adherence to TEM.

Both questionnaires were pilot tested. The questionnaire for patients was pilot tested among five couples who had been counselled for TEM in two hospitals. The questionnaire for professionals was pilot tested among two gynaecologists, three fertility doctors and two PhD students from two hospitals. The three parts of the questionnaires were well understood by all participants of the pilot study and therefore only minor modifications were made to the final version of the survey.

Statistical analysis

To quantify which barriers and facilitators the patients and the professionals experienced, the five point Likert scale responses were recoded into 3 point classification as 1=not agree, 2=neutral or 3=agree and the percentages per barrier or facilitator were calculated.

The barriers and facilitators were categorised per domain, i.e. the domain of the intervention, professional, the patient and the clinic (Cabana et al. 1999; Grol and Grimshaw 2003). For the statistical analyses the sum scores for each domain were calculated. To assess the internal consistency of those sum scores a Cronbach $\alpha$was calculated for each sum score. If the Cronbach $\alpha$was <0.5 a factor analysis was performed.

The characteristics of the participants, hospitals and the sum scores of the barriers and facilitators were tested for univariable relationship with the reported appreciation of TEM (patients) and adherence to TEM (professionals). The reported appreciation of TEM and the reported adherence to TEM served as the dependent variable. To evaluate the influence of the pregnancy status of the couple, i.e. not pregnant, natural conception or treatment in the TEM period, we included this variable in the analysis. We considered variables with $p \leq 0.15$ to be eligible for the multivariable variable regression analysis. Interaction analysis was performed between the variables included in the multivariable model and in case of significant

interaction ($p<0.05$) the interaction-terms were included in the multivariable model. In the multivariable analyses the variables with a $p<0.05$ were considered statistically significant. Statistical Products Service and Solutions (SPSS) PASW 18.0 was used for all analyses.

Ethical approval

Subjects did not undergo additional investigations nor treatment. As assessed by the Institutional Review Board (IRB), Academic Medical Center Amsterdam, the study was not subject to the Dutch "Medical Research Involving Human Subjects Act" (meaning that no formal IRB approval was needed).

RESULTS

Patients

We sent questionnaires to 195 couples who had been counseled for TEM, of whom 142 (73%) returned their questionnaire. Of these 142 couples, 24 couples did not fill in the questionnaire: 16 couples had not been advised TEM, five couples declined to fill in the questionnaire without a given reason, one couple split up, one woman had surgery for endometriosis and one couple terminated their wish for a child. This left 118 couples that filled in the questionnaire of whom 31 (26%) couples were not pregnant in their TEM period, 54 (46%) conceived in their TEM period, 11 (9%) started treatment in their TEM period and 22 (19%) had already finished their TEM period, and had treatment thereafter. The latter group (n=22) was excluded from the analysis because, as mentioned in the method section, their appreciation might have been biased by their failure to become pregnant and needing treatment. The flowchart of the patients is depicted in figure 1.

Patient characteristics of the included couples are summarized in Table 1. The mean age of the female and male participants was 32 and 35 years, respectively. The mean reported appreciation of TEM was 5.7 on a 10 point scale (Table 1).

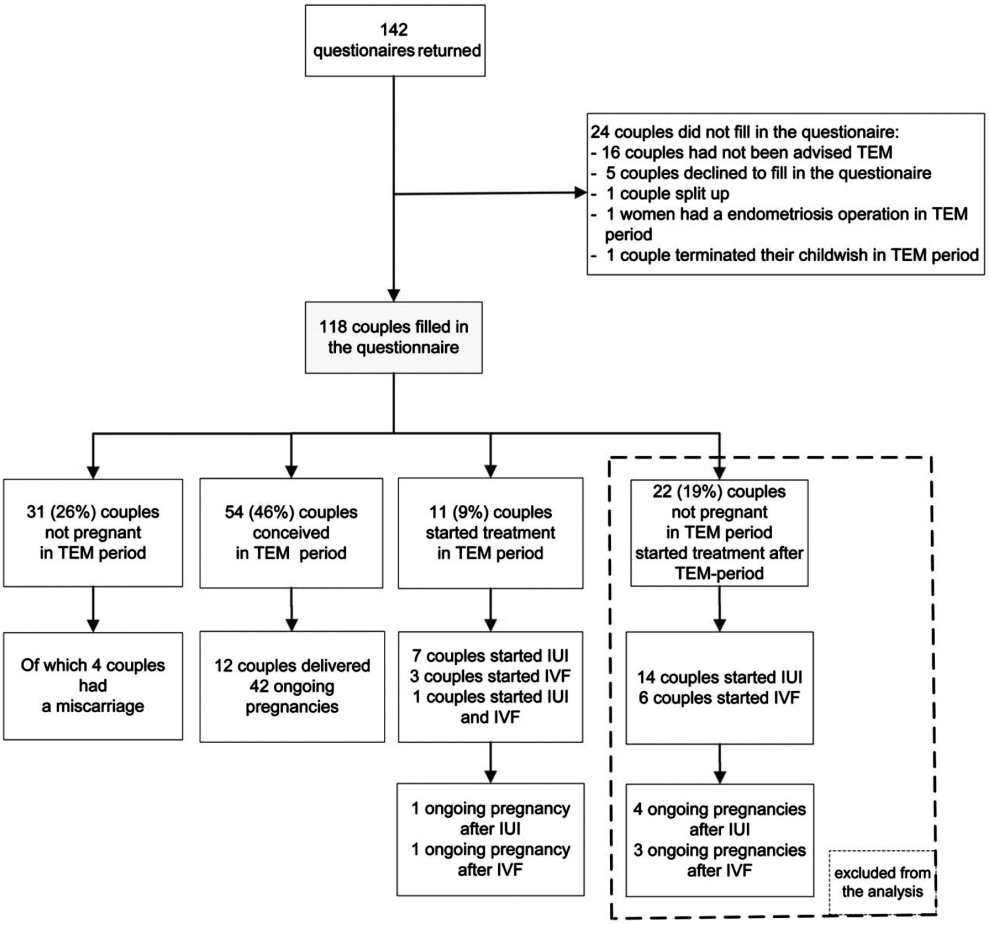

Figure 1. Flowchart of the pregnancy status of patients at the time the couples filled in the questionnaire. TEM: tailored expectant management, IUI: intra uterine insemination.

Table 1. Characteristics of the included couples (n = 96)

Patient characteristics (n = 96)		**Female**	**Male**
Mean age in years (SD)		32 (4.0)	35 (4.5)
Ethnic background	Dutch (%) overall	86 (90%)	84 (88%)
	Non-Dutch (%)*	10 (12%)	12 (13%)
Level of education**	Low	6 (6%)	10 (10%)
	Medium	33 (34%)	24 (25%)
	High	57 (59%)	60 (63%)
			Couples
Type of hospital	Academic		8 (8%)
	Non-academic		88 (92%)
Duration subfertility at first hospital visit, months, median (IQR) ***			13.4 (7.0)
Mean self-reported prognosis (SD) ****			42.5 (13.0)
Mean appreciation of TEM (1-10) (SD)			5.7 (2.2)

* The place of birth of the patient or both parents is outside the Netherlands, excluding its dominions

** Low: primary school / intermediate vocational education, Medium: higher general secondary education pre-university secondary education, High: higher vocational education / university

*** Duration between start conception-focused intercourse and first consultation fertility care

**** Chance of natural conception within 12 months according to the prognostic model of Hunault (Hunault et al. 2004)

Table II. Barriers and facilitators for TEM experienced by subfertile couples,
(b) = barrier (f) = facilitator. * happy, relieved, ** sad, disappointed, angry and expelled

Percentage of couples that perceive this as a barrier (b) or facilitator (f)	Couples n= 96
Characteristics of the intervention	
Lack of confidence in the natural conception (b)	85 (89%)
Knowledge of the factors used in the prognostic model (b)	75 (78%)
A need for more instructions about TEM period (b)	45 (47%)
A need for more information material about prognosis and TEM (b)	39 (41%)
Characteristics of the professional	
Preference for being informed about the option of TEM during the first consultation (f)	42 (44%)
Comparing spontaneous pregnancy chance with treatment (f)	29 (30%)
Unclear way of counselling and communicating chances (b)	9 (9%)
Characteristics of the patient	
Expected to get a cause for the subfertility (b)	84 (88%)
Expected to get treatment (b)	27 (28%)
Expected to get a cause for the subfertility and treatment (b)	19 (20%)
First reaction to prognosis and subsequent TEM:	
positive*	43 (45%)
negative**	28 (29%)
mixed feelings: happy and disappointed	66 (69%)
Understanding that with good prognosis, treatment was not indicated (f)	85 (89%)
Twin is a welcome complication despite the risks (b)	76 (79%)
Knowledge that good prognosis was reason for TEM (f)	74 (77%)
Inability to remember prognosis (b)	52 (54%)
Progressing female age (b)	52 (54%)
Longer duration of subfertility (b)	63 (66%)
Expected that with treatment >50% of all couples conceive (b)	43 (45%)
Expected to have a good spontaneous prognosis and not needing treatment (f)	36 (38%)
Characteristics of the clinic	
Other clinics offering reproductive treatment (b)	12 (12%)

Table III. Multivariable relationship between patients' appreciation of TEM and the patient characteristics, the barriers and facilitators of the four domains. Variables with $p<0.15$ in the univariable analyses were selected for the multivariable analysis.

Multivariable association between the patients' appreciation of TEM and patient characteristics, barriers and facilitators	P- value
Domain of the intervention	
Need for patient information about prognosis and TEM, sum score	0.047
Domain of the professional	
Not informing the couple about the option of TEM during the first consultation	0.955
Comparing natural conception chance with treatment	0.124
Domain the patient	
Understanding that with good prognosis, treatment was not indicated	0.810
Domain of the clinic	
Practice in other clinics	0.463

The percentages of couples that experienced a barrier or facilitator are summarized in Table II. In the domain of the intervention itself a majority of the couples reported a lack of confidence in the desired effect of natural conception and were aware of the factors used in the prognostic model. Almost half of the couples reported a need for more instructions or information material for the TEM period. In the domain of the professional almost half of the couples preferred being informed about the option of TEM during the first consultation and one third of the couples found it helpful if the chances of a natural conception were compared with the chances of a treatment related pregnancy. Prior to the first consultation a majority of the couples expected to get a diagnosis after the fertility work up and one third of the couples expected fertility treatment. Most couples had a positive or mixed first reaction on the advise for TEM. Understanding that treatment was not indicated and that good prognosis was the reason for TEM was reported by a large majority of the couples.
The Cronbach alphas of the sumscores of the domain of the intervention, the domain of the professional and the domain of the patient, were <0.5. For that reason a factor analysis was performed and the following sumscores showed internal consistency: the sumscores 'Need for patient information about prognosis and TEM' (Cronbach α0.83) and 'Complexity of the prognostic model' (Cronbach α0.63). The sumscore 'Need for patient information about prognosis and TEM' includes the barriers 'a need for more instructions for the TEM period' and 'a need for information material about prognosis and TEM'. The sumscore 'Complexity of the prognostic model' includes the facilitators 'knowledge of the factors used in the prognostic model', 'knowledge that good prognosis was reason for TEM' and 'understanding

that with good prognosis, treatment was not indicated'. The domain of the clinic contained only one barrier, so for this domain no Cronbach alpha was calculated.
The univariable analyses between the couples' appreciation of TEM as the dependent variable and patient' characteristics and the barriers and facilitators as the independent variable selected five variables for multivariable analysis: the sumscore of the need for patient information about prognosis and TEM, not informing the couple about the option of TEM during the first consultation, comparing natural conception chance with treatment chance, understanding that with good prognosis treatment was not indicated and the sumscore of practice in other clinics. Pregnancy status did not influence patients' appreciation of TEM in the univariable analysis. Interaction analysis showed no significant interaction between the included variables. Multivariable analysis showed a negative correlation between the reported appreciation of TEM and the need for more patient information about prognosis and TEM ($p=0.047$). The other four variables did not influence patients' appreciation of TEM (Table III).

Professionals

In total 117 of the 167 (70%) invited professionals filled in the online questionnaire. The professionals were from all 12 regions and had been trained in all 8 academic centres in the Netherlands. Baseline characteristics of the professionals are summarised in Table IV. A minority of the professionals were male (33%), the mean age of the professionals was 45, 45 (39%) were fertility doctors and the mean years of experience was 11. The mean reported adherence to TEM was 63%.
The percentages of professionals that experienced a barrier or facilitator are shown in Table V. In the domain of the intervention criticism on prognostic models, like missing factors was the most experienced barrier. The Body Mass Index and tobacco use were mentioned as missing factors in the prognostic models.
In the domain of the professional him/herself, the barriers forget to use the model and difficulties in counselling and communicating chances were experienced most frequently. None of the professionals experienced financial barriers for TEM.
In the patient domain the professionals experienced advancing female age, urgency for action expressed by the couple, couples expecting immediate treatment after the fertility work up and couples with a history of miscarriage(s) as main barriers.
The facilitators experienced most frequently were: local consensus among colleagues, a regular fertility meeting where subfertile couples are discussed after the fertility work up and the availability of a local protocol regarding the use of prognostic models and TEM.
The Cronbach alphas of the sumscores of the domains, i.e. the domain of the intervention, the domain of the professional, the domain of the patient and the domain of the clinic were 0.55, 0.66, 0.69 and 0.68 respectively.
Univariable analyses between the reported adherence to TEM as the dependent variable and the professional characteristics and the sum scores of the four domains as the independent

variable, selected six variables for multivariable analyses: type of physician (fertility doctor), a professional frequently seeing fertility patients, a local protocol, local consensus, a regular fertility meeting and the sumscore of the barriers in the domain of the professionals (Table VI). Interaction analysis of the included variables showed significant interaction between a regular fertility meeting and the sum score of the facilitators in the domain of the clinic. An interaction-term of those two variables was developed and included in the multivariable model. Multivariable analyses showed a positive correlation between the reported adherence to TEM and the professional being a fertility doctor instead of a gynaecologist (P= 0.041) and a non significant correlation with the facilitators in the domain of the clinic (P= 0.091). The sumscore of the barriers in the domain of the professional showed a negative correlation with adherence to TEM (P=0.008).

Table IV. Characteristics of the professionals (n= 117)

Characteristics of the professionals and the clinic	***n* = 117**
Male	39 (33%)
Mean age in years (SD)	45 (±9.7)
Fertility doctor (%)	45 (38%)
Mean years of experience (SD)	11 (±8.5)
University hospital	37 (32%)
Teaching hospital	55 (47%)
Non-teaching hospital	23 (20%)
Private clinic	2 (2%)
Local protocol available	73 (62%)
Fertility meeting	96 (82%)
Mean Self reported adherence to TEM (range)	63% (1-100%)

Table V. Barriers (b) and facilitators (f) for practice TEM experienced by professionals.

Percentage of professionals that perceive this as a barrier (b) or facilitator (f) for TEM	
	Professionals n=117
Domain of the intervention	
Incompleteness of the prognostic model (b)	47 (40%)
Not convinced about the model and the expectant management (b)	34 (29%)
The use of the model takes time (b)	19 (16%)
Domain of professionals	
Forget to use the model (b)	42 (36%)
Difficulties in counselling and communicating chances (b)	21 (18%)
Limited knowledge about the prognostic models and TEM (b)	20 (17%)
Close relation with the couple (b)	19 (16%)
Not (always) have access to the model (b)	15 (13%)
Treatment will generate income (b)	0 (0%)
Domain of the patient	
Advanced female age Urgency for action in the couple (b)	94 (80%) 87 (74%)
Expectations' of immediate treatment after the fertility work up (b) Couples with a history of miscarriage(s) (b)	69 (59%) 42 (36%)
Domain of the clinic	
Local consensus (f)	110 (94%)
A regular Fertility meeting (f)	104 (89%)
A local protocol (f)	98 (84%)
Centralisation of fertility care (f)	84 (72%)
Electronic Patient Dossier (f)	68 (58%)

Table VI. Multivariable relationship between professionals' self-reported adherence to TEM and the professional' characteristics, barriers and facilitators of the four domains. Variables with $p<0.15$ in the univariable analyses were selected for the multivariable analysis.

Multivariable association between the professionals' reported adherence to TEM and the professional' characteristics, barriers and facilitators	**P value**
Professional and Clinical characteristics	
Type physician: fertility doctor	0.041
Regular seeing fertility patients	0.195
Local protocol	0.981
Local consensus	0.380
Fertility meeting	0.667
Sum score** barriers in the domain of the professional	0.008
Sum score** facilitators in the domain of the clinic	0.091
Interaction term fertility meeting * sumscore clinic	0.374

Discussion

This nation wide study quantified patients' and professionals' considerations for treatment or expectant management. We found that patients' appreciation of TEM was moderate and may be improved by developing adequate patient information material, since this was a factor increasing patients' appreciation of TEM. Professional adherence to expectant management was moderate as well and may be improved by implementing regular fertility meetings and local protocols and by better knowledge and communication skills of professionals, since these were factors influencing professionals' adherence to TEM.

A strength of this study is that both questionnaires were based on determinants identified by previous qualitative research (van den Boogaard et al. 2011b). The step from best evidence to best practice needs various strategies targeting obstacles to change at different levels. Plans for change have to be based on the barriers and facilitators for change (Curran et al. 2008; Grimshaw et al. 2004). The high response rates and the large geographical spread of participants provided us with a representative setting. In a previous patient preference study, subfertile couples preferred IUI with or without stimulation above expectant management, if the treatment independent pregnancy chance in the next 12 months was lower than 50% and lower than 40%, respectively (Steures et al. 2005). Our study provides insight in their reasons for this preference and creates possibilities to improve the implementation of TEM.

This study is not without limitations. First, both patients and professionals may have given socially desirable answers. Second, a selection bias may have occurred as couples with a good outcome could have been more willing to respond and professionals not familiar with the model may have been less likely to respond. Taken these two limitations into account,

appreciation of and adherence to TEM can be lower in real life, which only emphasizes the importance of this study. Finally, as all data collection was carried out in the Netherlands, the reported findings may not be generalisable to other countries. However, the barriers and facilitators we quantified were not specifically related to the Dutch setting and we therefore consider our results applicable for an international setting, if the reimbursement system is comparable. In countries where the incomes depend on how many couples the doctor treats, this would obviously overrule all other barriers and facilitators of TEM. In countries where patients have to pay for their fertility treatment themselves, this financial argument works the other way around. In these countries TEM could become an important strategy, and knowledge of the barriers and facilitators of TEM is also then valuable.

This is not the first study that found that subfertile couples are not always content with expectant management. In our previous qualitative study in which we performed in depth interviews with couples who were counselled for TEM, we identified many dissatisfied couples (van den Boogaard et al. 2011b). In that qualitative study we concluded that patients did not really understand the reasons for expectant management but in this nation wide survey patients reported a good understanding of the reasons for expectant management. This discrepancy may be explained by a 'social desirability response bias' in the survey: it is possible that patients did not want to admit they did not understand the prognostic models and the reasons for the expectant management. This probably explains the need for more information and instructions about the prognostic models and the expectant management period, and provides a clear focus for improving implementation.

Forty-five percent of the couples who filled in the questionnaire conceived naturally in the TEM period, which confirms their good prognosis and the reason for the expectant management, which is in line with previous studies (Brandes et al. 2011; van der Steeg et al. 2007a).

Before the first visit to the hospital almost 90% of the couples expected that a cause for their subfertility would be found, a third of the couples expected immediate treatment after the fertility work up and a quarter of the couples expected both. At the same time, a majority of the professionals experienced couples' urgency for action and expectations for treatment as a barrier. It is thus likely that better knowledge of patients' expectations improves communication and counselling, and eventually improves adherence to TEM. In clinical practice this may imply offering training to professionals to improve communication skills.

The moderate professional adherence to the expectant management strategy is in line with one of our previous studies, in which a considerable percentage of couples were treated despite a good prognosis. In the same study we also saw a higher adherence in clinics where a fertility doctor was working (van den Boogaard et al. 2011a).

The wide range in the reported use of TEM (0-100%) demonstrates a large variation between the professionals. This variability of guideline adherence between professionals corresponds

with the results of other implementation studies in Dutch fertility care (Mourad et al. 2008; van Peperstraten et al. 2008a)
Since we found a clear association between patients' appreciation of TEM and professionals' adherence to TEM and the barriers and facilitators, a targeted strategy is likely to improve the implementation of TEM and to decrease harmful and costly overtreatment. This strategy has to focus on the development of adequate patient information material, implementing regular fertility meetings and a local protocol in a clinic and by teaching and training professionals to improve their communication skills and knowledge concerning TEM.

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Author's contributions

N.M. van den Boogaard contributed to the design of the study, analysis and interpretation of the data and she drafted the manuscript. A.M. Musters contributed to the design of the study, the analysis of the data and she contributed to the revisions of the manuscript. S.W. Bruhl and Tamara Tankens contributed to the acquisition and analysis of the data. J.A.M. Kremer contributed to the revisions of the manuscript and F. van der Veen, B.W.J. Mol, W.L.D.M. Nelen and P.G.A. Hompes contributed to the design of the study, interpretation of the data and to the revisions of the manuscript.

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Conflict of interest

None declared.

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Chapter 5

Improving the implementation of tailored expectant management in subfertile couples: a cluster randomized trial

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ABSTRACT

Background

Prognostic models in reproductive medicine can help to identify subfertile couples that would benefit from fertility treatment. Expectant management in couples with a good chance of natural conception, i.e. tailored expectant management (TEM), prevents unnecessary treatment and is therefore recommended in international fertility guidelines. However, current implementation is not optimal, leaving room for improvement. Based on barriers and facilitators for TEM that were recently identified among professionals and subfertile couples, we have developed a multifaceted implementation strategy. The goal of this study is to assess the effects of this implementation strategy on the guideline adherence on TEM.

Methods/Design

In a cluster randomized trial, 25 clinics and their allied practitioners units will be randomized between the multifaceted implementation strategy and care as usual. Randomization will be stratified for IVF facilities (full licensed, intermediate/no IVF facilities). The effect of the implementation strategy, i.e. the percentage guideline adherence on TEM, will be evaluated by pre- and post-randomization data collection. Furthermore there will be a process and cost evaluation of the strategy. The implementation strategy will focus on subfertile couples and their care providers i.e. general practitioners (GPs), fertility doctors and gynecologists. The implementation strategy addresses three levels: (1) Patient level: education materials in the form of a patient information leaflet and a website; (2) Professional level: audit and feedback, educational outreach visit, communication training and access to a digital version of the prognostic model of Hunault on a website; (3) Organizational level: providing a protocol based on the guideline. The primary outcome will be the percentage guideline adherence on TEM. Additional outcome measures will be treatment-, patient- and process-related outcome measures.

Discussion

This study will provide evidence about the effectiveness and costs of a multifaceted implementation strategy to improve guideline adherence on TEM.

Trial registration

www.trialregister.nl NTR3405. This study is sponsored by ZonMW.

Background

Subfertility is defined as the absence of conception after one year of unprotected intercourse (Zegers-Hochschild et al. 2009). It affects approximately 9% of all couples of reproductive age (Boivin et al. 2007 and Gnoth et al. 2003) In approximately 50% of the couples, no major cause is found after the basic fertility work-up (ECW Group, 2009). In those couples the chance of natural conception can be calculated via validated prognostic models (Hunault et al. 2004 and van der Steeg et al. 2007). If the chance of natural conception within one year is good, meaning a probability of 30% or more, expectant management for 6-12 months is equally effective as treatment (Steures et al. 2008). Since this expectant management is restricted to couples with a good prognosis, we have called it tailored expectant management (TEM).
European Society of Reproductive Medicine (ESHRE) and National Institute of Health (NICE) guidelines on the management of infertility both emphasize that couples should not be exposed to unnecessary risks or ineffective treatments and encourage that each subfertile couple should receive information about the estimate of their chance of natural conception (ESHRE guidelines infertility 2001 and NICE guidelines, 2004). In the Netherlands the national network guideline on infertility for gynecologists and general practitioners (GPs) explicitly the use of prognostic models and subsequent TEM for couples with unexplained or mild infertility (NHG and NVOG). However, at this moment, implementation of TEM is poor. A recent Dutch multicenter cohort study showed overtreatment in 36% of the couples, i.e. 36% of the couples with a good prognosis eligible for TEM (> 30% chance of natural conception in one year) already started medically assisted reproduction (MAR)(van den Boogaard et al. 2011a).
This overtreatment in subfertile couples is worrisome for several reasons. First, fertility treatment still leads to a considerable number of multiple pregnancies, which are associated with a higher morbidity and mortality in both mothers and neonates(Helmerhorst et al. 2004). Second, fertility treatment carries a significant physical and psychological burden and accompanying productivity loss (Verberg et al. 2008, Verhaak et al 2002, Bouwmans et al. 2008, Custers et al. 2012). Third, fertility treatment and its complications are expensive and put considerable financial strain on societies where MAR is reimbursed or on the subfertile couples in societies where MAR is not or only partially reimbursed.
The first step to improve guideline adherence on TEM and reduce overtreatment is to gain insight into barriers and facilitators for implementation of TEM and MAR reduction. Subsequently a tailored implementation strategy can be developed targeting obstacles to change, if necessary at different levels (Curan et al 2008. And Grol et al. 2003). In a previous qualitative and quantitative study among patients and professionals the main barriers among subfertile couples were lack of confidence in natural conception, perception that expectant management is a waste of time, inappropriate expectations prior to the first secondary care consultation and an overestimation of the success rates of treatment. Both couples and professionals regarded the lack of patient information materials as an important barrier. Among the professionals, limited knowledge about prognostic models and limited

communication skills to convince the couple, both leading to a decision in favor of treatment were recognized as main barriers. Facilitators experienced by the professionals were better management of patients' expectations, local consensus and the presence of a local protocol and local fertility meetings (van den Boogaard et al. 2011a and van den Boogaard et al. 2011b).
A multifaceted implementation strategy to improve guideline adherence on TEM has now been developed based on these data. The aim of this study is to evaluate effectiveness and costs of this implementation strategy in a cluster randomized trial.

METHODS

Setting

In the Netherlands, subfertile couples are usually referred by the general practitioner (GP) to secondary care. GPs usually perform only limited basic fertility workup or no workup at all and they do not prescribe fertility drugs. Secondary and tertiary care is provided by three different types of fertility clinics based on the kind of treatment they offer. Initial fertility assessment, ovulation induction (OI) and intra-uterine insemination (IUI) are carried out in all Dutch clinics. IVF and ICSI treatments are only carried out in intermediate and licensed fertility clinics.
Every Dutch citizen has a basic insurance coverage, which fully reimburses all treatment cycles of OI and IUI, with or without controlled ovarian hyperstimulation, as well as a maximum of three IVF or ICSI cycles.

Study design

We propose a cluster randomized trial in 25 clinics and their allied GP units with an effect, process and economic evaluation alongside the trial.

Randomisation

The 25 participating clinics and their allied practitioners units will be randomized between the multifaceted implementation strategy and care as usual. Randomization will be stratified for IVF facilities (full licensed, intermediate/no IVF facilities) and will take place after all clinics have approval to participate. Randomisation will be done be done by an independent physician and will be computer-generated. Results of the randomization will be personally communicated to all participating clinics.

Effectiveness

For the effectiveness, a baseline measurement will be performed in all participating clinics, including guideline adherence on TEM, and a range of organizational, professional and patient characteristics (see outcome measures). Following baseline measurement the multifaceted implementation strategy will be applied in the intervention clinics. After ten to twelve months of intervention exposure, the after measurement will be performed again in all 25 participating clinics.

Process evaluation

A process evaluation, according to Hulscher et al. (Hulsher et al. 2003), will be performed during and after the intervention to investigate the feasibility of the implementation strategy.

Intervention

The multifaceted implementation strategy, based on a barrier analysis among professionals and patients, will focus on three different levels: patient, professional and organizational level (van den Boogaard et al. 2011b). The three levels and all associated tools are successively described here.

Patient level:

We will develop patient educational materials in three different forms, a patient information leaflet, posters and a website.

The patient information leaflet will provide general background information on the fertility work-up procedure, prognostic factors that influence the chance on spontaneous conception, (dis)advantages of expectant management and (dis)advantages of fertility treatment. In every intervention clinic posters with information on the prognostic model and expectant management will be placed in the waiting areas. In the leaflet and on the posters patients can find a code which is needed to gain access to the website. There is a different code for each intervention clinic. The website will give more individualized information by access to a digital version of the prognostic model of Hunault (Hunault et al. 2004). Herewith patients can calculate their chances of natural conception within one year and experience the influence of altering characteristics. It will also provide additional information on the basic fertility workup, the chance of natural conception versus the chance of conception after fertility treatment, (dis)advantages of expectant management and (dis)advantages of fertility treatment. Furthermore, it advises patients what they can do to optimize their chances of spontaneous conception during the expectant management period, e.g. information on intercourse timing and frequency, weight regulation and lifestyle. This information will be

in accordance with the information provided in the Dutch national network guideline on infertility (NHG and NVOG).
This information material will be developed according to the *International Patient Decision Aids Standards* criteria for the dimensions 'information' and 'probabilities' (Elwyn et al. 2009) as well as according to the American Medical Association criteria (Winker et al. 2000).

Professional level (e.g. gynecologists (in training), fertility doctors and GPs)

The strategy regarding the professionals contains 1) audit and feedback, 2) an education outreach visit, 3) supportive consultation tools and 4) a video-based communication training. The audit and feedback of the current care will consist of a feedback report based on the results of the baseline measurement. This feedback will report clinic's guideline adherence on TEM in a twelve month period prior to the randomization compared with the other participating clinics. It will give insight in how they are adhering to the guideline concerning the policy for couples with unexplained or mild infertility, e.g. use of prognostic models and subsequent TEM in case the prognosis is good. Furthermore the report will provide feedback on patient related measures like general experiences with fertility care, specific experiences with the prognostic model and tailored expectant management, quality of life and trust in their physician.
In addition to this audit and feedback, an educational outreach visit will take place with fertility doctors and gynecologists (in training), in which background information about how and when to use the prognostic model of Hunault and subsequent TEM will be given and in which the results of the baseline measurement and local barriers will be discussed. The result of this visit will be an individualized action plan per clinic.
The supportive consultation tools are developed containing a digital version of the prognostic model of Hunault on a website and we will provide professionals with a summary of the guideline on TEM in the form of a pocket card.
Finally, a video-based training strategy will be provided to improve the communication techniques to counsel the patients on their chance of spontaneous conception versus conception after treatment, the (dis)advantages of expectant management versus fertility treatment and on the reason of TEM (i.e. making clear it is not a waste of time). Consistent with functional models of medical communication described in the field (de Haas et al. 2009), the LEAPS Framework, a pneumonic for Listen, Educate, Assess, Partner and Support will be used to develop the intervention (Roter et al. 2012).

Organizational level (GP units and fertility clinics).

During the educational outreach visits an example of an up to date local protocol will be offered to the fertility clinics, who do not already have an updated protocol available.

This local protocol will be based on the Dutch network guideline on infertility and it will focus on the initial fertility assessment (diagnostics), identification of patients with mild or unexplained infertility, the use of the prognostic model of Hunault and TEM. The clinics can adjust this protocol to their own lay out and they can distribute it either in the form of a hard-copy or digital-copy, depending on the preference of the professionals.
Furthermore we will provide the GPs allied to the intervention clinics with feedback on their referral behavior, e.g. were patients referred according to the guideline recommendations.

Study population/Participants

To include a representative patient group, we will select potential participating couples retrospectively in each clinic by means of the clinics' financial registration database (Diagnosis Treatment Combination code). In this nationwide registration system, patients undergoing diagnostics or treatment for infertility are identified with a specific Fertility-code (F-code). For the baseline measurement we will invite couples that were given the code for new fertility patients (F-11) between February 2011 to March 2012 to participate in this study. For the after measurement we will invite the couples that were given the F-11 code during the ten to twelve month intervention period. We will invite couples to participate by giving their permission for a medical record study and filling out a questionnaire.
The couples are eligible to participate when they have been diagnosed with unexplained or mild infertility, have a good prognosis (>30%) according to Hunault's prediction model, did not have previous fertility treatment and the female age is between 18 and 38 years. Couples with bilateral tubal pathology, severe male factor or anovulation are not eligible to participate.

Sample size

The expected adherence to TEM in the control arm is estimated based on previous studies at 60% (van den Boogaard et al. 2011a). To increase this to 80% with an Intra Class Correlation (ICC) of 0.1, alpha at 5%, comparing 2 strategies, we estimate that with 25 clusters we would need a total sample size of 450 patients. This means we need to include 15 to 20 patients per clinic in the baseline as well as in the after measurement.

Outcome measures

Primary outcome effectiveness

The primary outcome measure of the proposed study for effectiveness will be the guideline adherence rate on TEM: the percentage of couples that are eligible for TEM (couples with mild or unexplained infertility with a prognosis of >30% of natural conception within one

year) who actually agree upon the expectant management period of at least six months after the initial fertility assessment is concluded.

Secondary outcomes effectiveness

- Treatment related measures like time to the start of fertility treatment and the number and types of fertility treatments that the couples received.
- Treatment outcome related measures like (ongoing) pregnancy rate, miscarriage, extra uterine gravidity, multiple pregnancy rate and time to pregnancy.
- Patient related outcome measures like general experiences with fertility care such as information provision, respect for patients' values and accessibility of care (to be measured with Patient Centeredness Questionnaire Infertility) (van Empel et al. 2010), specific experiences with the prognostic model and tailored expectant management, quality of life (estimated by FertiQoL)(Aarts et al. 2011) and trust in physician (measured by Wake Forest Trust Scale) (Bachinger et al. 2009).
- Process related measures like percentage transition of patients to another fertility centre.
- Background characteristics that could influence guideline adherence (e.g. age, referral status, type of infertility, duration and cause of infertility).

Outcomes process evaluation

- Actual 'exposure' of patients and physicians to the different elements of the implementation strategy
- How frequently the website has been visited by patients and physicians
- Experiences of patients and physicians with the different elements of the implementation strategy.

Data collection

Effectiveness

Data collection will be performed from medical records and a patient questionnaire.
Data abstraction from medical records will be performed using a standardized audit form. We will collect the background characteristics, treatment related measures, treatment outcome related measures and process-related measures.
The questionnaire will be divided into four parts. The first part consists of background questions (e.g. highest educational level, country of birth). The second part regards the patients' experience with the prognostic model and tailored expectant management as well as the patients' trust in both the general practitioner as well as the fertility doctor/gynecologist. The third part is the Patient- Centeredness Questionnaire - Infertility, a validated instrument

measuring patient-centeredness of fertility care by asking about patients' experiences with care. The last part is the FertiQol questionnaire, We will only use the Core module which involves questions about Mind-Body, Emotional, Relational and Social aspects.

Process evaluation

For the process evaluation we will approach the local investigator, during the intervention period, to provide us with feedback about the implementation strategy. We will also keep track of how often the website is visited by logging data. At the end on the ten to twelve month intervention period we evaluate the strategy by means of a professional questionnaire and an addendum to the patients' questionnaire in the after measurement.

Data analysis

To analyze the effectiveness of the implementation strategy, descriptive statistics and multilevel analysis will be used. The statistical analysis will be performed using SPSS version 16.0 for Windows.
The main outcome, the difference in baseline and after-measurement scores in guideline adherence on tailored expectant management, between the intervention and control group will be analyzed with the chi-square test.
Descriptive analysis will be used to assess the difference in treatment related, treatment-outcome related and patient related measurements between the intervention and control group. Furthermore, time to pregnancy and time to start fertility treatment will be analyzed using Kaplan Meier analysis with log-rank test. Univariate and subsequent multivariate logistic and Cox regression analyses will be used to analyze the relative contribution of the implementation strategy versus other predictive factors for guideline adherence on TEM.

Economic evaluation

We plan an economic evaluation alongside the clinical trial to investigate the cost-effectiveness of the multifaceted implementation strategy to improve guideline adherence on TEM. This economic evaluation compares the multifaceted implementation strategy to usual care and is done from a societal perspective. A distinction will be made between costs of the development and introduction of the implementation strategy and the costs of maintaining the implementation strategy. The input of resources is assessed by collecting volumes of consumed resources (e.g. medical interventions like number IUI and IVF cycles and treatment related outcomes like ovarian hyperstimulation syndrome and multiple pregnancies) and multiplied by reported or guideline prices according to Oostenbrink (Oostenbrink et al. 2004). To asses non-medical and indirect costs we will build on the data collection and cost calculation frameworks from previous cost studies on IUI and IVF (Haagen et al. 2012 and Fiddelers et al. 2009). The incremental costs, expressed as costs/percentage

guideline adherence to TEM, are determined by the differences in resource consumption and adherence rates between the intervention group and the control group. Robustness of the results (costs and health outcomes) for various assumptions and parameters estimates will be explored in sensitivity analyses and visualized in ICER-graphs and cost-effectiveness acceptability curves.

Trial status

We are currently performing the baseline measurement in all participating clinics.

Discussion

This cluster RCT will compare a multifaceted implementation strategy to usual care on improving guideline adherence to TEM. If TEM is more applied, it will reduce the number of performed IUI, IVF and ICSI cycles, the incidence of treatment related complications (e.g. ovarian hyperstimulation syndrome and multiple pregnancies) and we expect it reduces the physical and psychological burden. As a consequence the costs for fertility treatment will decrease.

Many different interventions are available to implement guidelines, either focusing on professionals, patients, teams or organizational factors and with variable effects. A systematic review on interventions to improve guideline implementation showed that interventions tailored to prospectively identified barriers are more likely to improve professionals practice than only dissemination of guidelines (Ivers et al. 2012). The strategy that we developed is tailored to the recently identified barriers and facilitators for TEM, thus more likely to improve professionals practice, in this case: adherence to the guideline. Moreover, in general combined interventions are believed to be more effective than single interventions (Grimshaw et al. 2004). Therefore, to increase the potential effectiveness of our implementation strategy, we developed a multifaceted intervention that targets the specific barriers for TEM at different levels.

For the specific interventions that will be used in the multifaceted implementation strategy the review showed that: audit and feedback and educational outreach visits can be effective (small to moderate) (Grimshaw et al. 2004, Ivers et al. 2012) and patient-directed interventions such as educational materials may result in moderate to large effects to increase adherence to recommended care (Grimshaw et al. 2004). Moreover, it has been proven that subfertile patients appreciate education and improved knowledge and it has also been demonstrated to influence their healthcare decisions (Mourad et al. 2011 and Kreuwel et al. 2012). In a systematic review, only the effect of paper version materials was studied. However, because surveys have shown that online health information retrieval and eHealth activities are becoming increasingly common, especially within young and high educated subfertile

patients (Aarts et al. 2012, den Breejen et al. 2012, Weissman et al. 2000 and Haagen et al. 2003), we decided to offer the patient information materials in both paper and digital forms (i.e. website and application). By doing so, and thus tailoring the patient-directed intervention to the infertility population, we hope to increase the effect of this intervention even more.

Aside from the multifaceted and barrier tailored aspects of the strategy, this study has several more strengths;
First, the number of participating clinics is a great strength of this study. A quarter of all Dutch clinics from all over the country participate in this study, ensuring the representativeness of the Dutch infertility population as well as the professionals who provide fertility care.
Second, the process evaluation provides us with more information on the effectiveness and usefulness of the different interventions used in the strategy and not only of the multifaceted implementation strategy as a whole. We know that the multifaceted aspect of the intervention does not necessarily make the intervention more effective, therefore we need to assess the effectiveness of each individual intervention separately as well (Kreuwel et al. 2012). This is of great value for further implementation research and development of implementation strategies. Furthermore, if the multifaceted implementation strategy proves to be effective, it could also be generalized to improve implementation of other guidelines.
Third, the cost evaluation that will take place is very important from a societal aspect. Nowadays healthcare is becoming increasingly expensive and cost reduction is a very important and common topic in most governments and health care institutes. This economic evaluation will provide further information on how we can reduce costs in healthcare by following the current and already existing guidelines for best practice and care.

A possible limitation of the study is the chance of contamination of the GPs between the intervention and control group. GPs can refer patients to more than one clinic, this makes it possible that a GP who is allied to an intervention clinic can also refer patients to a control clinic. However we think that the occurrence of actual contamination will be very small because the participating clinics are very well spread over the country. In case contamination of GPs does occur, we expect the effect on the outcome to be very small or even undetectable because the multifaceted intervention strategy is mostly targeted at the secondary and tertiary care.
In summary, the main contribution of this study is that it seeks to identify the most effective strategy for implementing the guideline on tailored expectant management in subfertile couples. Ensuring the appropriate uptake of guideline recommendations by both professionals and patients will improve the care for these patient.

Abbreviations

(TEM): Tailored Expectant Management; (ESHRE): European Society of Reproductive Medicine; (NICE): National Institute of Health and Clinical Excellence; (NVOG): Dutch Society for Obstetrics and Gynecology; (MAR) Medically Assisted Reproduction.

Competing Interest

The author(s) declare that they have no competing interests.

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Authors' contributions

BWM, WLN, PGH, FvdV, DB, RH, FAMK, and NvdB were involved in conception and design of the study. NvdB, FAMK and WLN drafted the first manuscript. All authors read and approved the final manuscript and are local investigators in the participating centers.

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PART TWO:

Applicability of prognosis of natural conception

Chapter 6

Accessing fertility treatment in New Zealand: a comparison of the clinical priority access criteria with a prediction model for couples with unexplained subfertility

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ABSTRACT

BACKGROUND: In New Zealand, public funding for assisted reproductive technology (ART) is restricted to subfertile women who are unlikely to conceive spontaneously, based on clinical and social criteria known as the clinical priority access criteria (CPAC-score). The objective of this study was to compare this CPAC score with a prediction model for predicting spontaneous conception, developed in the Netherlands (the Hunault model).

METHODS: We performed a cohort study and included couples with unexplained subfertility and assessed the measure of agreement and the performance of the CPAC score and the Hunault prediction score.

RESULTS: Of 663 couples referred, 249 (38%) couples had unexplained subfertility. Of 246 women with follow-up data, there were 143 (58%) who had a live birth or ongoing pregnancy during the follow up period, 65 (26%) after fertility treatment and 78 (32%) after natural conception. There were 100 couples (41%) who had a Hunault prediction score of < 30%, which is the Dutch treatment threshold and 36 (15%) couples who had a CPAC score of >65, which is the New Zealand threshold for publically funded treatment. There were 69 couples (28%) who meet the threshold for treatment in the Netherlands but did not meet the New Zealand threshold for public funding. The kappa coefficient as a measure of agreement of the two scores and their treatment thresholds was 0.30 suggesting a fair agreement. The area under the curve (AUC) for the CPAC and Hunault scores were both 0.63, but the Hunault model performed better in calibration.

CONCLUSIONS: The CPAC score correlates fairly with the Hunault prediction score although using the Hunault prediction model 26% more couples would be recommended for ART. The discriminative capacities of both scores were comparable, but the Hunault prediction score performed better in calibration. Funding models in New Zealand should consider treating those women with unexplained subfertility who are least likely to conceive spontaneously.

Introduction

Having a baby is an important goal for many couples. However, after one year of regular protected intercourse about 10% couples will not have conceived and can be considered to be subfertile (Taylor 2003). After investigation, ~30% of couples have no definitive cause of subfertility identified, which is known as unexplained subfertility, and many of these couples will seek assisted reproductive technologies (ART) (Boivin et al. 2007; Collins and Van 2004). However, in most countries there are limitations in public health funding for ART because of cost (Chambers et al. 2009). In New Zealand, an approach has been developed that aimed to provide public funding for those couples with the greatest need to receive fertility treatment (Farquhar and Gillett 2006; Gillett et al. 2011). For the past decade, public funding in New Zealand has been restricted to infertile couples who are unlikely to conceive spontaneously, who are aged < 40 years old, have a body mass index < 32 kg/m^2 and who do not smoke cigarettes (Gillett et al. 2006; Gillett et al. 2011). In addition, seven separate criteria were developed for the clinical priority access criteria (CPAC) score, each having subcategories for which points were weighted reflecting the need and also the benefit obtained from ART treatment (Appendix 1). The CPAC score increases as the duration of subfertility becomes longer (reaching a maximum by ≥5 years) but decreases at 40. The highest score possible is 100 points and the threshold for access to publicly funded ART is set at ≥65 points. Couples with unexplained subfertility appear to be at the most disadvantage as they must have had 5 years of subfertility in order to reach the threshold of ≥65 points.

In recent years there has been increased interest in prediction models for fertility treatments. A systematic review of 29 prediction models (Leushuis et al. 2009) reported that there were three models with good predictive performance; of these, the Hunault model dealt with prediction of treatment independent pregnancy with unexplained subfertility (Hunault et al. 2004; Steures et al. 2004; Templeton 2000). The Hunault model has been validated in a large study of more than 3000 couples (van der Steeg et al. 2007a). This model has proven useful in helping clinicians to identify the likelihood of spontaneous pregnancy and to more effectively recommend fertility treatment or expectant management (Appendix 2). When the calculated prognosis on a spontaneous pregnancy is ≥30% likelihood of conceiving within 12 months, tailored expectant management is a cost effective strategy that prevents overtreatment, complications and costs (Steures et al. 2006). Therefore, expectant management in couples with a good prognosis is now recommended in the Dutch guidelines for management of infertile couples (NVOG guidelines 2009).

This study sought to consider whether the New Zealand approach to fund fertility treatment for couples with unexplained fertility was based on the best prognostic factors and how this New Zealand approach differs from the Dutch approach. The objective of this study was to evaluate the measure of agreement between the CPAC score and the Hunault prediction

score and to compare the performance of both scores, using a NZ cohort of couples with unexplained subfertility.

Methods

We included couples who were referred by primary care for their first fertility specialist appointment to Fertility Plus (a specialist fertility clinic of National Women's Health of the Auckland District Health Board that offers public and private care) between January 2007 and December 2008 and who were diagnosed with unexplained subfertility. The criteria for unexplained fertility were that the woman had to have at least one patent fallopian tube, ovulation confirmed with a luteal progesterone test, and a regular menstrual cycle. Menstrual cycles were defined as regular if they were between 23 – 35 days in length, with a variation of less than 8 days. Female exclusion factors were anovulation, significant adhesions or endometriosis greater than grade 2 (as judged by the revised AFS classification). A male exclusion factor was a total motility count of less than 10 million sperm cells.

The CPAC score was calculated from criteria each having subcategories for which points were weighted, reflecting the need and also the benefit obtained from ART treatment (Gillett et al. 2006; Gillett et al. 2011; Hadorn and Holmes 1997; Elective Services 2001). The criteria included a diagnostic score derived from the subfertility diagnosis intended to reflect the probability of spontaneous pregnancy, the woman's age, the woman's basal FSH, whether the woman smoked or not, the duration of the couple's subfertility, the number of children, whether either partner had been sterilized or not and the main cause of subfertility (ovulation disorders, endometriosis, other tuboperitoneal disorders and male factor). A longer duration of subfertility and a higher female age increases the CPAC score, but if the female's is ≥40, the CPAC score decreases. The highest score possible is 100 points and the threshold for access to publicly funded ART is set at ≥ 65 points (http://humrep.oxfordjournals.org/content/26/11/3037/T3.expansion.html). The CPAC score is structured in such a way that couples require a minimum duration of subfertility of 1 year before potentially being eligible for access to publically-funded ART. In New Zealand, women who smoke and women with a body mass index (BMI) of ≥32 are immediately ineligible for publically funded ART. Once a couple has 65 points or more then they are eligible for two cycles of IVF or 8 cycles of intrauterine insemination or a combination of 4 cycles IUI and 1 cycle IVF. After a couple has reached eligibility, there is typically a further 12 month wait for cycle commencement.

The parameters used for the Hunault prediction score are female age, the duration of subfertility, the proportion of progressive motile sperm, the referral status and the subfertility being primary or secondary. Approximately half of the semen analyses were done at the on-site fertility laboratory and included progressive motility data and the remainder were completed at a community laboratory that only reported total motility. To account for this difference the mean difference between total and progressive motility was calculated from

the results where both were reported (12.4%) and this percentage was subtracted from the total motility where progressive motility was not reported.

Data on subsequent fertility treatments and pregnancies resulting in live births after a couple's specialist appointment were collected. If no data was available in the electronic medical record, then a letter was sent to the woman requesting information on pregnancy outcomes. Ethics Committee approval was received for this last part of the study that required contacting patients directly to ascertain pregnancy status (NTY/10/EXP/058 of the Northern Y Ethics Committee of the New Zealand Ministry of Health).

Univariate analysis was used to compare demographic and fertility characteristics between couples with a spontaneous live birth, a treatment related live birth and couples without a live birth. Comparisons between continuous, bivariate and categorical variables were analysed with the one way ANOVA, the Kruskall-Wallis and the Chi-square respectively. The measure of agreement between the two scores and treatment thresholds was assessed by calculating a kappa coefficient. Discriminative capacity was assessed with receiver operation characteristics (ROC) analysis and the area under the curve (AUC) of the couples that conceived spontaneously within 12 months. Calibration was assessed by comparing the mean predicted probability of the CPAC score and the Hunault model with the mean observed fraction of spontaneous pregnancies at 12 months per percentile subgroup. Calculations were performed with SPSS 18. (Statistical Package for the Social Sciences: SPSS, Chicago, IL, USA).

Results

Of the 663 couples included in the study, 249 were diagnosed with unexplained subfertility and included in the study. Three of these women were lost to follow-up as they were known to have left the region. The mean age (SD) of all women was 33.5 (3.8) years, the mean BMI was 23.7 (3.5) kg/m^2, the mean (SD) length of trying to conceive was 21 (20.8) months and 35 (14%) couples had secondary subfertility. The median (IQR) CPAC score of all patients was 19.5 (35) and the mean (SD) Hunault prediction score was 32.3 (12.0).

Patient characteristics by pregnancy outcome are summarised in Table I. Of the 249 couples, 126 (50%) had fertility treatment during the follow up period. Of the 246 women with follow-up, 143 (58%) had a live birth, of which 65 (26%) as a result of fertility treatment and 78 (32%) were spontaneous conceptions. Of the 65 women who conceived as a result of fertility treatment, 40 (61%) underwent ART cycles, 13 (20%) received IUI with clomiphene and 12 (19%) conceived with clomiphene citrate. Of the 40 women who conceived with ART cycles, 29 received public funding for their treatment and the remainder were privately funded. The median CPAC score (IQR) was 16 (14) for women with a spontaneous conception, 25 (36) for women who conceived after treatment and 20 (34) for women who did not conceive ($P=0.004$). The mean Hunault prediction score (SD) for spontaneous conception was 36.1

(10.6), 30.7 (12.5) for couples that conceived after treatment and 30.6 (11.3) for women who did not conceive was (P=0.003). The median (IQR) time to conceive was significantly shorter in the women with spontaneous conceptions (8 (13) months) compared wit treatment related conceptions (18 (12) months) (P=0.004). The mean (SD) duration of subfertility was significantly greater in those women who conceived with treatment (34 (21) months) or did not conceive (36 (23) months) compared with those with spontaneous conception (25 (14) months (P=0.0001).

Table II summarises the characteristics and outcomes of the couples with CPAC score ≥ 65 and <65 and a Hunault prediction of score <30% and ≥ 30% chance on a spontaneous pregnancy, the treatment thresholds in New Zealand and the Netherlands respectively. There were 36 women (15%) who had a CPAC score ≥ 65 (the threshold which entitled them to receive publically funded fertility treatment), whereas 100 women (41%) had a Hunault prediction score of <30% (the treatment threshold according the Dutch fertility guidelines). The spontaneous live birth rates were significantly lower in the couples eligible for treatment according both treatment thresholds (P=0.004 CPAC-threshold, P=0.005 Hunault-threshold). The female age was higher and the duration of subfertility was longer in the couples eligible for treatment according both treatment thresholds (P= 0.014 and p< 0.0001 CPAC-threshold, p<0.001 and p<0.001 Hunault threshold, respectively). According to the CPAC treatment threshold and the Hunault treatment threshold, 31 (13%) couples would be recommended to receive fertility treatment in both countries, 141 (57%) couples would not receive treatment in either country, 69 (28%) couples would receive treatment in the Netherlands but would not receive treatment in New Zealand and 5 (2%) couples who would not receive treatment in the Netherlands but would receive treatment in New Zealand (Figure 1). The kappa coefficient as a measure of agreement of the two treatment selection strategies was 0.30, suggesting a fair agreement.

Table I. Characteristics of the study population [a] Note missing data for three women and for ethnicity [b] One way ANOVA, [c] Chi square, [d] Kruskall Wallis[e.] From first specialist, Appointment to 6 weeks pregnancy

	Women with spontaneous ongoing pregnancy [a] n=78	**Women with treatment related ongoing pregnancies [a] n=65**	**Women with no pregnancies n=103**	**p-value**
Mean female age (SD)	32.9 (3.5)	33.8 (3.5)	33.9 (4.2)	0.181[b]
Primary subfertility (%)	45 (58)	41 (63)	55 (53)	0.311 [b]
Duration of subfertility in months (median, IQR)	24.5 (13.8)	34.1 (21.0)	36.3 (23.6)	<0.001 [b]
One-sided tubal pathology HSG or laparoscopy (%)	7 (9)	6 (9)	14 (13)	0.557 [c]
Total Motility Count (median, IQR)	75.8 (124.35)	130.7 (97.49)	92.6 (103.75)	0.035 [d]
Ethnicity of woman, n (%) - European - Maori - Pacific - Asian - Indian - Other	 40 (51) 0 3 (4.2) 15 (21) 7 (9.9) 5 (7)	 43 (60.6) 1 (1.4) 2 (2.8) 11 (15) 9 (13) 5 (7)	 48 (47) 5 (5) 4 (4) 20 (18.9) 17 (16.8) 6 (5.9)	0.5884 [d]
BMI of woman (mean)	23.3 (2.9)	23.6 (3.4)	24.0 (3.8)	0.260 [b]
CPAC score (median, IQR)	16.0 (14)	25.0 (36)	20.0 (34)	0.004[a]
Women with CPAC score <65	74 (95)	53 (82)	83 (81)	0.016 [c]
Hunault prediction score (mean, SD)	36.1 (10.6)	30.7 (12.5)	30.6 (11.3)	0.003[b]
Women with Hunault predictionscore < 30	21 (27%)	29 (45)	50 (49%)	0.019 [c]
Time to conceive in months [e] (median, IQR)	8 (13)	18 (12)	-	<0.001[d]

Table II. Features and outcomes of couples with CPAC score ≥ 65 and <65 and a Hunault prediction (Hunault) of score <30% and ≥30% chance on a spontaneous pregnancy [a] Missing data = three women who moved from the district. IQR: interquartile range

	Treatment threshold	Expectant management threshold	p-value
New Zealand	**CPAC score ≥ 65 (n=36)**	**CPAC score <65 (n=210)**	
Mean female age (SD)	35.0 (2.9)	33.3 (3.9)	0.014
Duration of subfertility in months (median, IQR)	60.0 (17)	24.0 (18)	<0.001
Couples with Hunault prediction score <30%, n (%)	31 (86)	69 (33%)	<0.001
Couples with a spontaneous livebirth, n (%)	4 (11)	74 (35%)	0.004
Couples received treatment, n (%)	24 (67)	92 (44%)	0.013
Couples with live birth after treatment, n (%)	12 (50)	53 (25%)	0.504
Total live birth, n (%)	16 (44)	127 (60%)	0.063
The Netherlands	**Hunault score <30% (n=100)**	**Hunault score ≥30% (n=146)**	
Mean female age (SD)	35.8 (2.8)	32.0 (3.7)	<0.001
Duration of subfertility in months (median, IQR)	36 (36)	24 (4)	<0.001
Couples with CPAC score ≥ 65, n(%)	31 (31)	5 (3.4)	<0.001
Couples with a spontaneous ongoing pregnancy, n (%)	22 (22)	56 (38)	0.005
Couples received treatment, n (%)	55 (55)	61 (42)	0.028
Couples with ongoing pregnancy after treatment, n (%)	29 (45)	36 (55)	0.496
Total live births, n (%)	51 (51)	92 (63)	0.047

The ROC curves of both scores are shown in Figure 2. The CPAC score and the Hunault prediction score both had an Area Under the Curve (AUC) of 0.63. The calibration plot in Figure 3 shows the association between the mean calculated CPAC score and the observed fraction of couples with a spontaneous pregnancy within 12 months in 4 percentile subgroups. Because a lot of couples had the same CPAC score the calibration could only be plotted in 4 subgroups which makes the calibration plot difficult to interpret: in 2 subgroups the calibration was good and in the other 2 subgroups the calibration was poor. Figure 4 shows the calibration plot of the

Hunault score, with the mean calculated probability on a spontaneous pregnancy on the X axis and the observed fraction of couples with an ongoing spontaneous livebirth within 12 months on the Y-axis, for each of the 10 decile subgroups. The calibration plot of the Hunault score was moderate but performed best in the couples with a prognosis <30%.

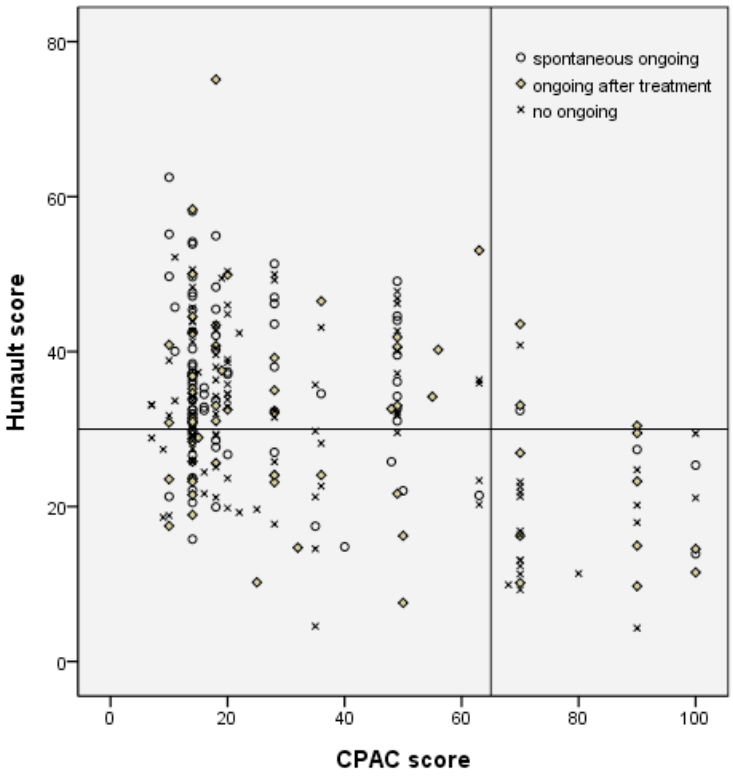


Figure 1 The correlation of CPAC score and the Hunault prediction model
The lines at the X-axis at 65 and at the Y axis at 30 represent the treatments thresholds for New Zealand and the Netherlands, respectively. In the lower right quadrant are the couples (n=31) who would receive fertility treatment in both countries, the upper left quadrant are the couples (n=141) would not receive treatment in either country. In the lower left quadrant there are couples (n=69) who would receive treatment according the Hunault prediction score but would not receive treatment according to the CPAC score and in the upper right quadrant are couples (n=5) who would not receive treatment according the Hunault prediction score but would receive treatment according to the CPAC score.

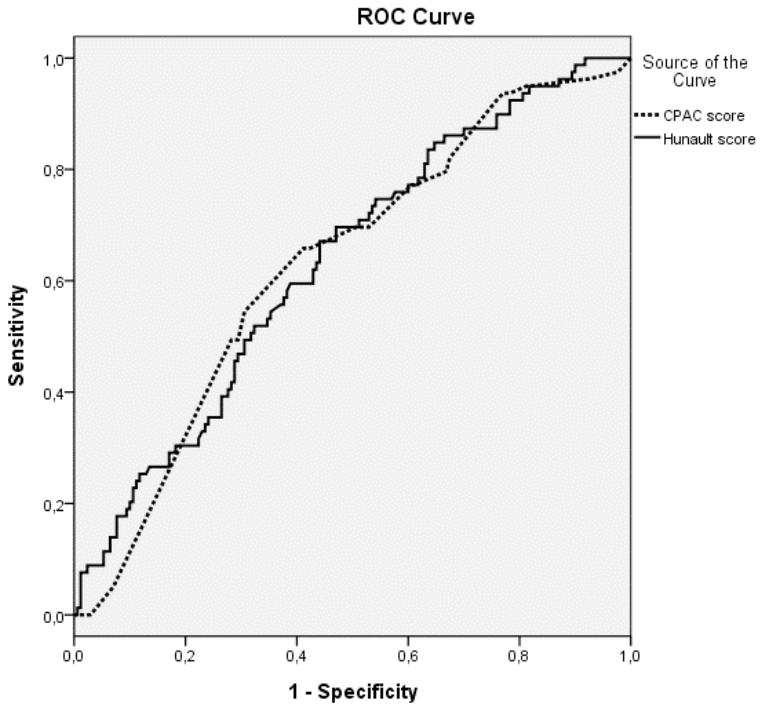


Figure 2 The AUC of the Hunault prediction score (Dutch model) is 0.632 and the AUC of the CPAC score (New Zealand) is0.629. Only the spontaneous pregnancies are included in this analysis

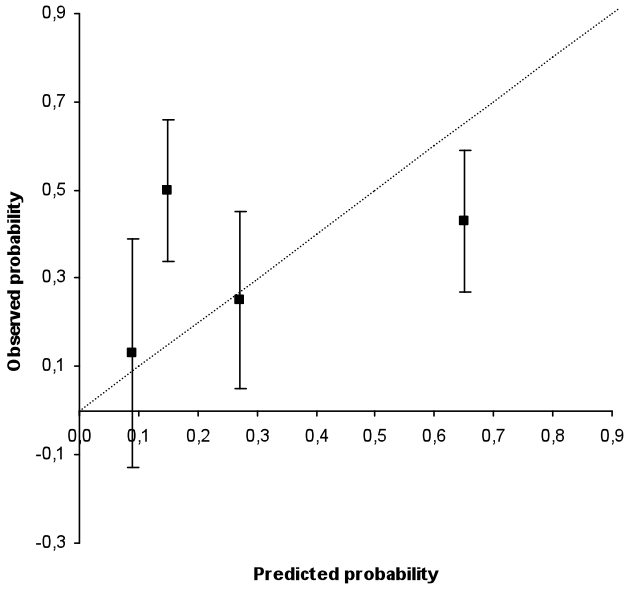


Figure 3. Calibration plot of the CPAC score of the couples with an spontaneous pregnancy within 12 months (n=79).

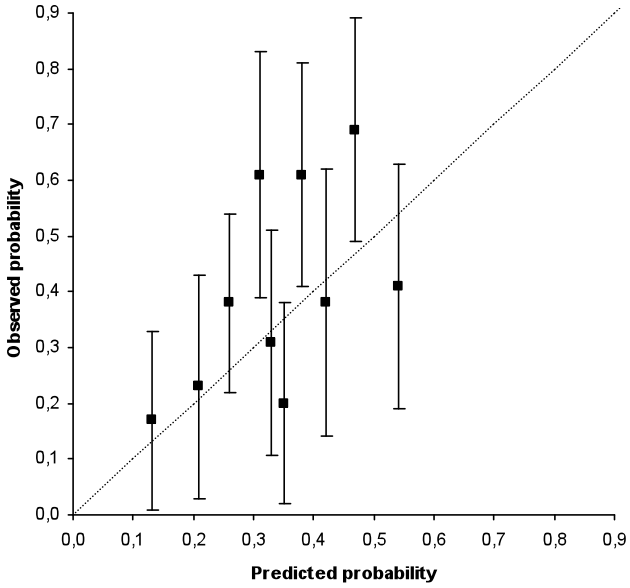


Figure 4. Calibration plot of the Hunault prediction model of the predicted and observed spontaneous pregnancies within 12 months (n=79)

Discussion

The current approach in New Zealand of using a CPAC score to determine access to treatment for couples with unexplained subfertility correlates only fairly with the Hunault prediction scores and there were 26% fewer couples eligible for publically funded treatment in New Zealand compared with the Netherlands. The AUC for both approaches implies moderate discrimination for the prediction of pregnancy but the Hunault score performed better for calibration than the CPAC score. The calibration plot of the Hunault score performed best in couples with a prognosis <30%. In evaluating the performance of prediction models in fertility care the AUC is low for most prediction models in reproductive medicine. However, low values of the AUC do not imply that these models are of limited use in clinical practice. The calibration of the model (the correspondence between model-based probabilities and observed pregnancy rates) as well as the availability of a clinically useful distribution of probabilities are more meaningful concepts for model evaluation (Coppus et al. 2009) In that regard, the Hunault prediction model performs better on both aspects (calibration and a clinically relevant distribution of the probabilities).

This study sought to consider whether the New Zealand approach to funding fertility for couples with unexplained subfertility was comparable to other prediction models. The study has compared the New Zealand scoring system for 249 couples with unexplained subfertility with a prediction score validated in more than 3000 couples and found that the CPAC scores correlated fairly with the Hunault prediction score. It has also shown that almost 70% of

women who met the criteria for funding in the Netherlands would not receive treatment with the CPAC system. For example, if it is accepted that the prediction model threshold of 30% identifies a population of couples who have a low chance of conceiving spontaneously, then it is unsatisfactory that only 14% of couples in this category have a CPAC scores ≥65 and would receive funded fertility treatment in New Zealand.

Overall, women with unexplained subfertility have a reasonable chance of conceiving either spontaneously or with treatment. In our study a third of couples with unexplained subfertility conceived spontaneously in the 4-5 years of follow up and the median time to conceive was 8 months from the time of the first consultation with almost half of them conceiving in the first year. When the women who conceived after treatment were included, then the proportion of women with a live birth was 57%. Overall the 57% of women who conceived in this study is lower than the 80% of women from the Netherlands with unexplained subfertility who conceived either spontaneously or with treatment within 36 months of their first specialist appointment (Brandes et al. 2011). The lower rates in New Zealand may in part be explained by the earlier presentation of women in the Netherlands as the mean duration of subfertility in the Dutch cohort study was 21 months compared to 32 months in New Zealand.

There are several limitations to our study. Follow up may be incomplete, as although we collected outcome data from two sources including electronic medical records and direct written contact with the patient it is possible that some treatment and pregnancy outcomes have been missed because of patients moving out of the region. Other differences between the two approaches are that some criteria in CPAC could be applied subjectively such as the stage of endometriosis, the extent of tubal adhesions and the extent of oligoamenorrhoea. In addition, the calibration model does not fit the CPAC approach well as CPAC tends to cluster scores and is therefore not a natural measure of continuous fertility outcomes. Finally, the CPAC score is not a prediction score as it increases with age but then decreases >40 years, yet we have compared it with a prediction model which makes the linearity for evaluation debatable. The strength of our study was that the CPAC scoring was independent as it was performed by the study investigator and not the clinician. In addition, the prediction model has been validated in more than 3000 couples with unexplained subfertility (van der Steeg et al. 2007a). Another strength of this study is that this is the first time the CPAC score is compared with a validated prediction model and it is the first time that the Hunault model has been validated in a New Zealand population.

Should New Zealand consider changes to the CPAC on the basis of this study? This study has shown that the CPAC model has performed poorly compared to the Hunault prediction model. On the other hand, in New Zealand only 15% of couples were recommended to receive publically funded treatment whereas using the Hunault prediction model 41% of couples would have been recommended to have treatment. The Hunault prediction model is based on robust evidence, in contrast to the CPAC score which was developed for funding reasons. An alternative to introducing the Hunault system would be to lower the threshold of 65 which would require additional funding. One of the challenges with the CPAC system is that

there is no difference in the score if you are 32 or 39 (all other things being equal), although it then ceases at the age of 40. As many of the women in this study were over 36 years old, then it can be argued that this older group should have priority over younger women. The Hunault system addresses the impact of age on spontaneous pregnancy and this is a further reason to consider using this model in New Zealand for women with unexplained subfertility. Whatever changes to the funding system are made it is clear that if more couples are treated then an increase in funding for fertility treatment will be needed. Treating those women who have a low prediction score makes both clinical and economic sense as with each additional year their chances of success with or without ART will decline.

APPENDIX 1: THE CPAC SCOREA.

Diagnostic score		
Ovulation	Anovulation 2 hypopituitary hypogonadism, ovulatory with treatment, not pregnant after 9 months	6
	Clomiphene ± metformin ± resistance to laparoscopic ovarian diathermy, oligo-ovulation/luteal defects (fewer than nine ovulatory cycles per year)	3
	No ovulation defect	0
Semen	Strict abnormal morphology, 10%/count <1 M motile/ml/severe Abs (mixed antiglobulin reaction over 40%)	6
	<1 M motile sperm after semen prep/IUI where <2 M motile recovered	
	3× IUI without conception where male factor but >2 M motile recovered	
	<50% motile or <20 million/ml on two occasions	3
	No sperm defect	0
Endometriosis	Stage IV	6
	Stage III	3
	Stage II	2
	Stage I	1
	No endometriosis	0
Tubal	Occlusion/severe adhesions/unsuccessful surgery after 12 months	6
	Moderate adhesions/unsuccessful surgery after 6 months	3
	Polyps/mild adhesions/normal tube on one side	2
	Minimal adhesions on best side	1
	No tubo-peritoneal pathology	0
Other factors	Severe	6
	Moderate	3
	Mild	2
	Minimal	1
	None	0
Duration of exposure to pregnancy	≥5 years	6
	≥4 and <5 years	3
	≥3 and <4 years	2
	<3 years	1

	Objective criteria	Points	Now	+1 year	+2 years
Diagnostic score (01) (see above)	Total score				
	≥6	1.0			
	3–5	0.7			
	2	0.4			
	0–1	0.2			
Woman's age (02)[b]	≤39 years	1.0			
	40, 41	0.5			
	≥42	0.1			
Objective score (OS)	OS = 01 × 02				
	Social criteria	**Points**	**Now**	**+1 year**	**+2 years**
Duration of infertility over time (S1)[c]	<1 year	5			
	1 or 2 years	20			
	3 or 4 years	40			
	5 years or more	50			
Children at home (S2)[d]	None	30			
	1 by relationship	10			
	>1 by relationship	5			
	By previous relationship	8			
Sterilization (S3)[e]	Neither partner	20			
	Yes, but death of child	20			
	Yes	10			
Social score (SS)	SS = S1 + S2 + S3				
Score	=OS × SS				

[a]In order to assess publically funded fertility treatment women must be aged <40 years old, non-smoking and have a BMI ≤32 kg/m^2. Only patients with a score of 65 or more can access fertility treatment in the next 12 months.

[b]A category for age is included to accommodate the possibility of lowering the threshold in the future.

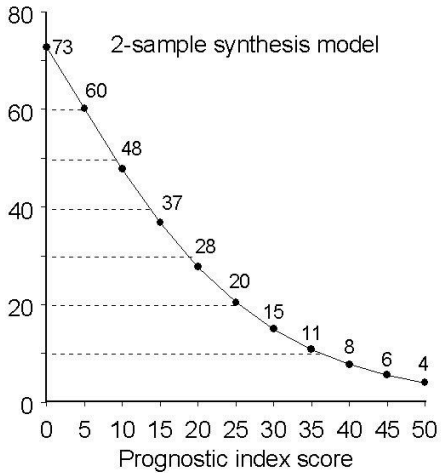
[c]The duration of infertility is cumulative over previous and current relationships except after sterilization reversal when duration is from when a child is planned in the current relationship.

[d]Children living at home are defined as children under the age of 12 who have lived with the couple for most of the child's life.

[e]Single and lesbian women are eligible for scoring is there is a clear biological cause of infertility or at least 12 cycles of DI with pregnancy of which 6 must be undertaken with in an accredited unit.

Appendix 2: The Hunault prediction score

							score
woman's age (y)	21-25	26-31	32-35	36-37	38-39	40-41	
score:	**0**	**2**	**6**	**9**	**11**	**12**	
duration of subfertility (y)	1	2	3-4	5-6	7-8		
score:	**0**	**2**	**5**	**9**	**13**		
type of subfertility			*secondary*	*primary*			
score:			**0**	**6**			
motility (%)	≥ 60	40-59	20-39	0-19			
score:	**0**	**2**	**4**	**6**			
referral status		*secondary-care couple*	tertiary-care couple				
score:		**0**	**4**				
post-coital-test			*normal*			*abnormal*	
score:		**0**	**14**				
			Prognostic Index Score (Sum) :				



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Chapter 7

The prognostic profile of subfertile couples and treatment outcome after expectant management, intrauterine insemination and in vitro fertilisation: a study protocol for the meta-analysis of individual patient data.

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ABSTRACT:

OBJECTIVE: The current evidence concerning the best treatment option for couples with unexplained and male subfertility is inconclusive. Most studies which have evaluated the effectiveness of treatment options like expectant management (EM), intra uterine insemination (IUI) with or without controlled ovarian stimulation (COS) and in vitro fertilisation (IVF), have not taken the couples' prognosis into account. It is very likely that the individual prognosis of the couple influences the effect of treatment. Individual patient data analyses allow us to take these prognostic factors into account and to evaluate their effect on treatment outcome. This study aims to use anonimysed data from relevant published trials to perform an individual patient data meta-analysis evaluating the effect of couples' prognosis on the effectiveness of EM, IUI with or without COS and IVF.

METHODS: Based on earlier systematic reviews and an updated search, randomised controlled trials will be considered for inclusion. Authors of the included studies will be invited to form a collaborative group to share their original anonymised data. The data will be assessed on validity, quality and completeness. The prognosis of the individual couple will be calculated with existing prognostic models. The effect of the prognosis on treatment outcome will be analysed with marker-by-treatment predictiveness curves, illustrating the effect of prognosis on treatment outcome.

POPULATION: Untreated subfertile couples with unexplained or male subfertility included in trials comparing EM, IUI with or without COS and IVF. This study is registered in PROSPERO (registration number CRD42011001832).

CONCLUSION: Ultimately, this study may help to select the appropriate fertility treatment tailored to the needs of an individual couple.

INTRODUCTION:

Subfertility affects at least 10% of couples trying to conceive (Gnoth et al. 2003; Wang et al. 2003). In approximately half of them, no major underlying cause is found (Aboulghar M et al. 2009). Although intrauterine insemination (IUI) with or without controlled ovarian stimulation (COS) is often the first step in the treatment algorithm in these couples, the evidence for the effectiveness of IUI with or without COS over expectant management (EM) remains inconclusive (Cohlen et al. 2005; Hughes 2003). The results of trials comparing IUI alone, IUI with COS or EM with each other, have been pooled in several meta-analyses (Bensdorp et al. 2007; Helmerhorst et al. 2005a; Steures et al. 2008; Verhulst et al. 2006).

A review on IUI for couples with unexplained subfertility showed a significant increase in pregnancy rates for treatment with both IUI and COS, separately. Data on multiple pregnancies and other adverse events for treatment with COS were insufficient to allow conclusions (Verhulst et al. 2006). A review on IUI for male subfertility concluded there was insufficient evidence to recommend IUI with or without COS above EM or vice versa (Bensdorp et al. 2007). A review including studies with unexplained, male and cervical subfertility found higher pregnancy rates for IUI and COS in couples with unexplained subfertility, but not in couples with good prospects on a spontaneous pregnancy. In couples with cervical factor and male subfertility, IUI alone led to higher pregnancy rates (Steures et al. 2008). However, the quality of the included trials was poor, the sample sizes were small, and complications like multiple pregnancies were poorly reported.

In Vitro Fertilisation (IVF) and Intra Cytoplasmic Sperm Injection (ICSI) were initially introduced to help couples with infertility due to the inability of the male and female gametes to meet or the inability of the spermatozoa to penetrate the egg. Nowadays, IVF and ICSI are also used for couples in whom these conditions are not met and who thus have a chance of natural conception. The effectiveness of IVF as primary treatment or after failed IUI in those couples is debatable. The pooled results of trials that compared IVF with expectant management or intrauterine insemination (IUI) with or without controlled ovarian hyperstimulation (COS) in couples with mainly unexplained or mild male subfertility are difficult to interpret due to the heterogeneity of the studies and lack of prognostic information about the couples in relation to treatment outcome (Pandian et al. 2010). In a cohort of newly referred subfertile couples, the contribution of IVF in couples with unexplained subfertility and ovulation disorders was extremely limited -ongoing pregnancy rates of 13 and 4.5%, respectively- compared to patients with tubal factor, endometriosis and male factor in whom pregnancy rates were 45, 45 and 37%, respectively (Brandes et al. 2010). Here, just like in the IUI studies, there was limited information about influence of prognostic factors on treatment outcome.

This information can be derived from prognostic models which estimate the chances of spontaneous conception (Hunault et al. 2004; van der Steeg et al. 2007a) or following fertility treatment (Custers et al. 2007; Steures et al. 2004; Templeton 2000). The use of these models can help to discriminate between couples who would benefit from intervention from those who would not.

When conventional meta-analyses are inconclusive or contradictory, individual patient data meta-analysis (IPD-MA) can have additional value, because it allows this very evaluation of prognosis on treatment effect. This is important, because it may well be that, if treatment is tailored to couples with a low chance of conceiving spontaneously, the treatment effect increases and vice versa. Therefore, we plan to perform an individual patient data (IPD) meta-analysis of randomized controlled trials evaluating the effect of couples' individual prognosis on the effectiveness of Expectant management (EM), IUI, both with and without COS and IVF.

Objectives of the study

The main goal of this study is to evaluate the effect of prognosis on the effectiveness of EM, IUI with and without COS and IVF in couples with mainly unexplained subfertility using IPD-MA. Mainly unexplained subfertility is defined as couples in which the gametes are able to meet, and includes couples with unexplained and male subfertility. The prognostic models we will use are the Hunault model (Hunault et al. 2004) that predicts the chance on a spontaneous pregnancy within 12 months, the models of Steures that predicts the chance on pregnancy after IUI with and without COS (Steures et al. 2004) and the model of Templeton that predicts the chance on pregnancy with IVF (Templeton 2000). Those models are selected because they are the only models that performed well in the external validation (Leushuis et al. 2009).
Hunault's model includes the predictors female age, duration of subfertility, subfertility being primary or secondary, percentage of motile sperm and the referral status. Steures' model includes female age, duration of subfertility, cervical factor, male factor, tuba pathology, uterus anomaly, endometriosis and the use of clomifene or recombinant -FSH. Templeton's model includes female age, duration of subfertility, tubal subfertility, livebirth after IVF, livebirth which was not a result of IVF, a previous pregnancy after IVF which did not result in a livebirth and a previous pregnancy not after IVF which did not result in a livebirth.

METHODS AND DESIGN

Literature-search and data sharing request

Previously, systematic reviews of trials comparing the included treatments-options for each diagnostic subgroup, i.e. unexplained, male and cervical factor subfertility, have been performed (Bensdorp et al. 2007; Helmerhorst et al. 2005a; Pandian et al. 2005; Steures et al. 2008; Verhulst et al. 2006). By means of these reviews we will identify studies for our IPD-meta-analysis. We will update the performed search strategies to include studies published up to date and we will check references and ask authors whether they are aware of unpublished ongoing studies. In case of a cross over design the authors will be asked if they have the pre-crossover data available separately. Readers of this protocol, who are familiar

with studies performed in this field that are not integrated in the previous performed meta-analyses, are also invited to approach us.

Registration

The protocol is registered with PROSPERO.com (registration number CRD42011001832).

Data acquisition

We plan to contact the first authors of the studies included by email and in case of no response we will also email the last authors. When there is still no reaction we will try to contact them by phone. We will ask them to send the complete anonimysed dataset as to minimise their efforts going through their dataset to select appropriate variables. We accept any data format, provided that variables and categories are adequately labelled within the dataset or with a separate dictionary. All participants will be identified by study number. Names and addresses will not be included in any of the datasets sent by the primary research groups. Anonymised data from relevant trials (the results of which have all been published in peer reviewed journals in the past), will be amalgamated and stored in a password protected University of Amsterdam Computer at the Amsterdam Medical centre Amsterdam and usual precautions regarding confidentiality and access will be observed. The dataset will not be used for any other research apart from that described in the protocol. The data will be stored for 5 years beyond the life of this project (2011-2013).

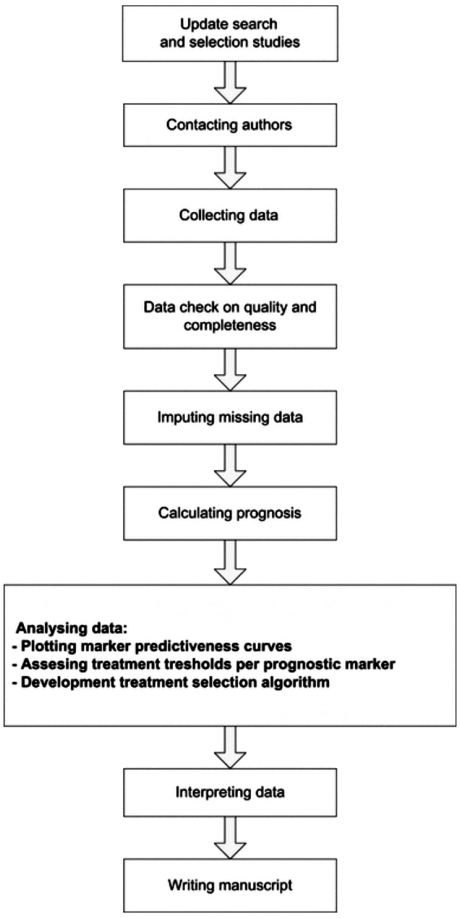

Figure 1. Flowchart of the study protocol

Quality assessment

For each trial, information on the quality of the trial will be extracted based on a number of items: adequate randomisation, concealment of allocation, parallel design and exclusions after randomisation. If a trial does not adhere to these standards, its validity will be considered as compromised. Depending on the level of the compromise, the randomised trial can be excluded in the analysis. If there is a large variety in quality and completeness of data between different trials, separate analysis will be made in high and poor quality trials next to analysing all data as a whole. The same treatment arms of the different trials will be assed on comparability. Completeness of the datasets in terms of prognostic markers and outcomes will be reported. The consistency of data and the published manuscript will be assessed. If data are missing or inconsistent or the details of the treatment are unclear, the original investigator will be contacted. Incomplete data or major inconsistencies with published

results can lead to exclusion. There is no strict limit set for the fraction of acceptable missing data, since this depends on which variable and the type of missing data. The decision to include or exclude a study will be discussed in the project group.

Analysis

All the different steps of this protocol are summarised in a flowchart, see figure 1. Before the start of the analysis, we aim to make the variable codes of all the acquired data compatible. Missing data will be imputed using multiple imputations within the original studies. All the prognostic factors will be used as predictors for the imputations. The prognosis of the patients will be calculated based on the prognostic models of Hunault, Steures and Templeton (Hunault et al. 2004; Steures et al. 2004; Templeton 2000). If heterogeneity allows, the original data will be merged into a single set. A study identification variable will be added to reflect the stratified nature of the pooled dataset.

Initial analyses will be performed for the primary outcome livebirth or ongoing pregnancy per couple, depending on the availability of the data. Secondary outcomes are livebirth or ongoing pregnancy per cycle and multiple pregnancies per couple. Livebirth is defined as the delivery of at least one living child beyond 22 weeks. Ongoing pregnancy is defined as the presence of fetal cardiac activity at ultrasound at a gestational age of ≥ 12 weeks. The baseline characteristics and the outcomes will be summarised in a table, per study and overall.

A marker-by-treatment predictiveness curve will be plotted per trial and per prognostic marker to illustrate the treatment effect as a function of the prognosis (Janes et al. 2011). The calculated prognostic variable will be used as the marker. If there is a differential benefit from treatment, these curves will show the treatment threshold for the prognostic marker. In that case, some patients benefit from treatment, whereas other do not, and the marker can be used to make the selection.

The effect of the prognostic marker based treatment strategy will be evaluated by comparing the outcome of treating all patients without taking the prognostic marker threshold into account versus treating couples according to the prognostic marker threshold (Vickers et al. 2007). Subsequently we will evaluate the proportion of patients for whom treatment recommendations would change after using the prognostic marker based treatment strategy (Oratz et al. 2007). Finally, we will compare the effects of the different prognostic marker-based treatment strategies on pregnancy outcomes.

If there is a relation between the treatment effect and the prognosis and the curves show a treatment threshold per prognosis, an algorithm will be developed for clinical practice. This algorithm will help the clinician to choose the best treatment strategy for the individual patient based on their prognosis.

Collaboration

Meetings

To have the opportunity to discuss the project with the co-authors, meetings at international fertility congresses will be organised. During these meetings the project in general and the practical, methodological and data related aspects can be discussed.

Authorship

We plan to provide one co-authorship for each contributor of individual patient data for the articles that we publish. In case the number of authors is limited by journal editors, we propose to publish under a collaborative group name. For articles explicitly focusing on methodological aspects of IPD-meta-analyses, where these data are used for illustratory purposes, contributors will be individually acknowledged in each article. The results of this project will be presented on international conferences and published in clinical and epidemiological journals.

Competing interests

Some of the authors are authors of the original trials on which the proposed IPD-MA is based.

Disclosure of interest

There are no conflicting interests in this study

Contribution to authorship

BWM is the principal investigator of this study. NB is responsible for the overall logistical aspects of this study, drafted the first version of this paper and will perform the analysis together with PT, PB, BM, FvdV, and PH. BM will supervise the whole process. SB, IC, AJG, DG, PS have agreed to share data and all authors read and approved the final article.

Details of ethical approval

We propose to use only anonymised data from published trials. In response to our query the Ethics Committee of the Academic Medical Centre in Amsterdam did not feel that formal Ethics Approval was required.

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Chapter 8

Prognostic profiles and the effectiveness of assisted conception: secondary analyses of individual patient data

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ABSTRACT

Background. At present, it is unclear which treatment strategy is best for couples with unexplained or mild male subfertility. We hypothesized that the prognostic profile influences the effectiveness of assisted conception. We addressed this issue by analysing individual patient data RCTs.

Methods. We performed an individual patient data (IPD) analysis of published randomised controlled trials (RCTs) on treatment strategies for subfertile couples. Eligible studies were identified from Cochrane systematic reviews and we also searched Medline and EMBASE. The authors of RCTs which compared expectant management (EM), intracervical insemination (ICI), intrauterine insemination (IUI), all three with or without controlled ovarian stimulation (COS) and IVF in couples with unexplained or male subfertility, and had reported live birth or ongoing pregnancy as an outcome measure, were invited to share their data. For each individual patient the chance of natural conception was calculated with a validated prognostic model. We constructed prognosis-by-treatment curves and tested whether there was a significant interaction between treatment and prognosis.

Results. We acquired data from 8 RCTs, including 2,550 couples. In three studies (n= 954) the more invasive treatment strategies tended to be less effective in couples with a high chance of natural conception but this difference did not reach statistical significance (p-value for interaction between prognosis and treatment outcome were 0.71, 0.31 and 0.19). In one study (n=932 couples) the strategies with COS (ICI and IUI) led to higher pregnancy rates than unstimulated strategies (ICI 8% vs. 15%, IUI 13% vs. 22%), regardless of prognosis (p-value for interaction in al comparisons >0.5), but at the expense of a high twin rate in de COS strategies (ICI 6% vs. 23% and IUI 3% vs. 30% respectively). In two studies (n= 373 couples), the more invasive treatment strategies tended to be more effective in couples with a good prognosis but this difference did not reach statistical significance (p-value for interaction: 0.38 and 0.68). In one study (n=253 couples) the differential effect of prognosis on treatment effect was limited (p-value for interaction 0.52), perhaps because prognosis was incorporated in the inclusion criteria. The only study that compared EM with IVF included 38 couples, too small for a precise estimate.

Conclusions. In this IPD analysis of couples with unexplained or male subfertility, we did not find a large differential effect of prognosis on the effectiveness of fertility treatment with IUI, COS or IVF.

INTRODUCTION

Despite the frequent use of fertility enhancing treatments in couples with unexplained or male subfertility, evidence from randomised trials is scarce. Most international guidelines recommend starting with less invasive treatments, for example intrauterine insemination (IUI), and moving on to more aggressive interventions, such as IVF, if these are unsuccessful or when the woman is older and the duration of subfertility is longer (The Practice Committe of the American Society of Reproductive Medicine, 2012;NICE, 2004;ESHRE, 2001).

Data from randomised controlled trials (RCTs) are contradictory and sometimes counterintuitive (Bhattacharya *et al.*, 2008;Goverde *et al.*, 2000;Guzick *et al.*, 1999;Hughes *et al.*, 2004;Reindollar *et al.*, 2010;Soliman *et al.*, 1993;Steures *et al.*, 2006). These studies do not provide a clear recommendation on which couple would benefit from which treatment. For example, in a comparison between IUI and expectant management (EM) there is a non-significant beneficial effect for IUI (odds ratio: 1.53 confidence interval (CI): 0.91-2.56) (Bhattacharya *et al.*, 2008), while in another comparison between IUI with controlled ovarian stimulation (COS) and EM there is no significant beneficial effect for IUI with COS (risk ratio (RR):0.85 CI: 0.55-1.30)(Steures *et al.*, 2006). In studies that compared IVF with EM one showed a significant beneficial effect of IVF over EM (RR 4,5, CI 1,44-14,6)(Hughes *et al.*, 2004), while another found a non-significant beneficial effect of EM (RR: 2,7 CI: 0.97-7.49) (Soliman *et al.*, 1993). Several meta-analyses have pooled the results of these RCTs and also did not find convincing benefits of one treatment strategy over the other (Bensdorp *et al.*, 2007;Steures *et al.*, 2008;Verhulst *et al.*, 2006;Veltman-Verhulst *et al.*, 2012). A possible explanation for this may be the inclusion of couples with varying prognostic profiles as evident from the wide range in female age and duration of subfertility within RCTs, which results in different chances of natural conception. When conventional meta-analyses are inconclusive or contradictory and the trials included are heterogeneous, individual patient data (IPD) analysis can have additional value, because factors influencing the outcome (in this case prognosis) can be taken into account in the analysis. As such, IPD is an extension of standard meta-analysis and may create new possibilities for evaluating treatments and treatment policies. In the Netherlands, standard treatment policy is to use the prognostic profile of a subfertile couple to select couples for EM. In the present IPD analysis we wanted to evaluate if this prognostic profile can be used to select couples for a specific treatment, such as IUI with or without COS or IVF. We evaluated if the treatment effects in the RCTs are influenced by the prognostic profile of the couples. We hypothesized that invasive treatments, such as IUI with COS or IVF, are more effective than EM in couples with limited chances of natural conception, but less so in couples with good prospects of natural conception. To test our hypothesis, we performed an IPD analysis of published RCTs, and evaluated whether a couples' prognosis of natural conception attenuated or strengthened the impact of assisted reproduction.

Methods

We performed an IPD analysis of published RCTs on treatment strategies for subfertile couples. The protocol has been published previously (van den Boogaard *et al.*, 2012). This study is registered in PROSPERO (registration number CRD42011001832) and the study protocol of this study is published in the BJOG.

Selection of studies

We selected studies in couples who had been trying to conceive for at least 1 year, were diagnosed with unexplained, male or cervical factor subfertility, and who had never received COS, IUI or IVF in the past. Unexplained subfertility was defined as subfertility without any demonstrable cause after the basic fertility work up, including tests of ovulation, semen analysis and tubal evaluation. Mild endometriosis and one-sided tubal pathology were also categorised as unexplained subfertility. For the definition of male subfertility the World Health Organization criteria of 2009 were used (Cooper *et al.*, 2010). The prognostic model used in our analysis includes the motility of the sperm as a predictor. This allows us to be liberal in the inclusion of studies with male subfertility. Cervical factor subfertility was defined as the absence of progressive motile spermatozoa in cervical mucus with normal semen parameters.

RCTs were eligible if they had compared two or more of the following strategies: EM, timed intercourse with or without COS, IUI with or without COS, or IVF and if they had reported live birth or ongoing pregnancy as an outcome measure.

We included only truly RCTs. Quasi-randomised studies, where allocation relied on alternation or chart number, were not eligible. In case of a cross-over design the authors were asked for the pre-crossover data.

Eligible studies were identified based on Cochrane systematic reviews of studies comparing EM, intra-cervical insemination (ICI) or IUI with and without COS and IVF in couples with unexplained, male or cervical factor subfertility (Bensdorp *et al.*, 2007;Helmerhorst *et al.*, 2005;Pandian *et al.*, 2005;Steures *et al.*, 2008;Verhulst *et al.*, 2006). We additionally searched Medline and EMBASE to detect trials published after closure of the data collection of the Cochrane reviews. We used the following search terms (with synonyms and closely related words): ‘infertility’, ‘subfecundity’, ‘unexplained subfertility’, ‘male subfertility’, ‘cervical factor’, ‘intrauterine insemination’ ‘intrauterine insemination with COS’ and ‘in-vitro fertilisation’. We did not apply language restrictions. The final search was performed in January 2011. References were checked and authors of relevant studies were contacted to ask whether they were aware of any unpublished ongoing studies.

Collection of IPD

For each eligible study, we tried to obtain contact information of the first author from Medline, EMBASE or from searching the Internet. We invited authors by email to share their data. If contact information of the first author was unavailable or when the first author did not respond after two or more emails, we contacted the second or last author.
We provided authors who were considering participation with a more detailed study proposal and asked authors to send us their complete database in original format, to minimize their efforts to select the appropriate variables or to convert data to a specific format. If variables and categories were not adequately labelled, a separate data dictionary was requested. The data received were crosschecked against published reports of the study. Authors were contacted for clarification in case of discrepancies and asked to supply any missing data when possible.

Data extraction

From each trial, we extracted information on the characteristics of the couples: female age, duration, type and cause of subfertility, previous miscarriages, percentage motile sperm, sperm concentration, grade of endometriosis, tubal patency, referral status, BMI, number of treatment cycles, number of follicles ≥16 mm during IUI , dose of gonadotrophins, number of embryos transferred; and the type of outcome, i.e. live birth, ongoing pregnancy and multiple birth.

Assessment of study quality

Assessment of the methodological quality of included studies was based on the information reported in the original published papers and responses to specific queries to the authors. We assessed the risk of bias assessed by checking the adequacy of randomisation, comparability of groups at baseline, the completeness of follow-up, and *a priori* sample size estimation. Generalizability was based on the description of the sample recruited. The adequacy of randomisation was assessed by checking methods used for sequence generation, treatment allocation and allocation concealment. When these details were unclear in the initial publication, we contacted authors to provide further clarification.

Analysis

For every RCT we calculated the chances of natural conception leading to live birth within 12 months for each participating couple, using the validated prognostic model developed by Hunault *et al.* (2004). This model takes into account female age, duration of subfertility, subfertility being primary or secondary, percentage of motile sperm and being referred by

a general practitioner or gynaecologist. Missing data were multiply imputed within each original dataset, using all prognostic factors and the outcome.
Using logistic regression we estimated the probability of live birth for each couple based on the Hunault score, the treatment allocation and an the interaction between the Hunault score and the treatment allocation. This interaction term explores whether the relation between the Hunault score and the treatment outcome. We evaluated the statistical significance of this interaction term with the Wald test statistic, using a conventional significance level of $P<0.05$. If live birth was not registered ongoing pregnancy was used.
We also graphically presented the regression model. We used a prognosis-by-treatment curve, similar to the marker-by-treatment predictiveness curves proposed by Janes *et al.* (2011). These graphs display for each treatment arm the probability of a live birth over the range of Hunault prognoses. When a differential benefit from treatment is present, the curves intersect: on the left side of the intersection the treatment line on top results in a higher number of live births, at the intersection point both treatments result in the same number of live births, this then switches and on the right side of the intersection the other treatment is favourable and results in a higher number of live births.
If heterogeneity allows, the original data will be merged into a single set and the abovementioned analyses will be performed for the merged data set as well.
Data were analyzed using the Statistical Package for the Social Sciences
18.0 (SPSS Inc., Chicago, IL, USA). A p-value < 0.05 was considered statistically significant.

Ethical approval

We used anonymised data. The Ethics Committee of the Academic Medical Centre in Amsterdam indicated that formal approval of an ethics committee was not required. Ethical approval to share trial data was obtained by participating trial groups in their centres if necessary.

RESULTS

Study selection

The systematic literature search and the results of the data sharing requests are summarised in a flowchart, figure 1. From previously published systematic reviews, 31 studies were selected as eligible. The additional literature search yielded 159 citations. Three full text manuscripts were further evaluated for eligibility, all had to be excluded for different reasons (Reindollar *et al.*, 2010;Streda *et al.*, 2007;Tummon *et al.*, 1997). One, not yet published study was included via co-authors of included studies (Custers *et al.*, 2011). The authors of 32 eligible studies, containing 4.460 couples in total, were invited to share their IPD (Table 1). Authors of 12 studies did not have the original data available (Agarwal *et al*., 2004;Aribarg

et al., 1995;Chung *et al.*, 1995;Cohlen *et al.*, 1998;Crosignani *et al.*, 1991;Crosignani *et al.*, 1994;Ho *et al.*, 1989;Ho *et al.*, 1992;Martinez *et al.*, 1990;Murdoch *et al.*, 1991;Nan *et al.*, 1994;te Velde *et al.*, 1989). The authors of 12 other studies did not respond to two or more emails (Arcaini *et al.*, 1996;Arici *et al.*, 1994;Deaton *et al.*, 1990;Glazener *et al.*, 1987;Gregoriou *et al.*, 1996;Janko *et al.*, 1998;Jaroudi *et al.*, 1998;Karlstrom et *al.*, 1993;Kerin *et al.*, 1984;Kerin *et al.*, 1987;Kirby *et al.*, 1991;Melis *et al.*, 1995). Eventually, the authors of eight of the 32 eligible studies contributed their data, containing data for 2,550 of the total 4,460 eligible couples. These eight studies were included in this IPD analysis (Bhattacharya *et al.*, 2008;Custers *et al.*, 2011;Goverde *et al.*, 2000;Guzick *et al.*, 1999;Hughes *et al.*, 2004;Steures *et al.*, 2006;Steures *et al.*, 2007a;Steures *et al.*, 2007b).

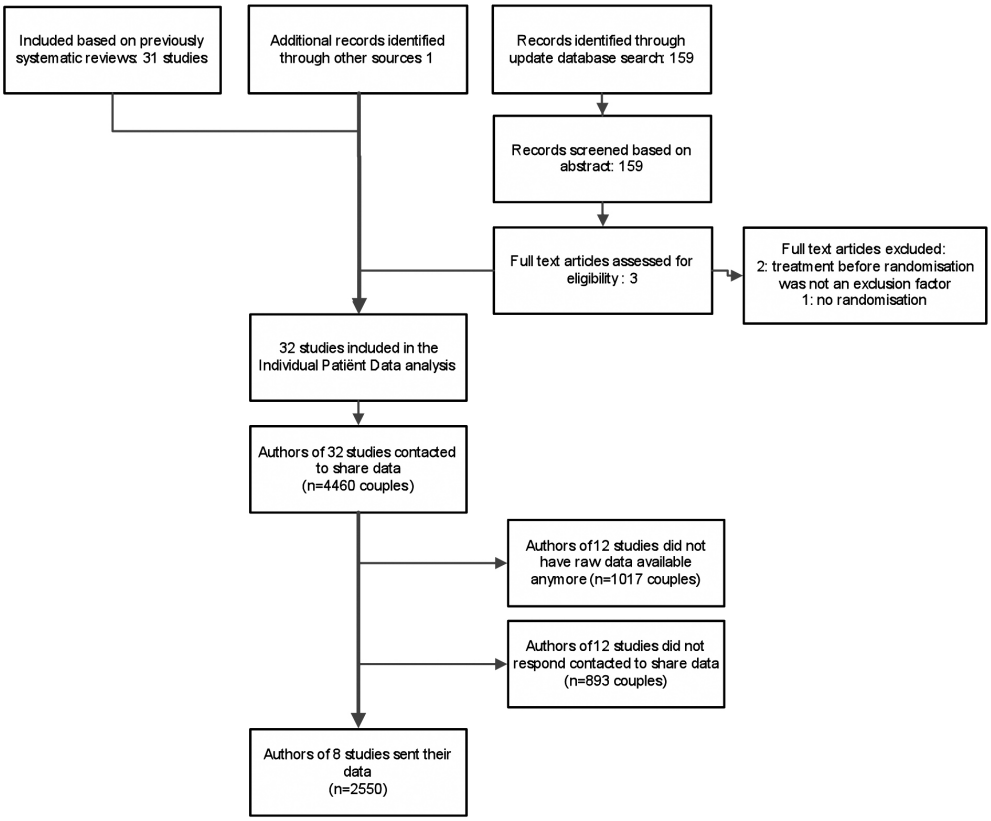


Figure 1. Flow diagram of study selection

Table 1. Eligilble studies

	Authors	Publication year
1	Agarwal et al.	2004
2	Arcaini et al.	1996
3	Aribarg et al.	1995
4	Bhattacharya et al.	2008
5	Chung et al.	1995
6	Cohlen et al.	1998
7	Crosignani et al.	1994
8	Crosignani et al.	1991
9	Custers et al.	2011
10	Deaton et al.	1990
11	Glazener et al.	1987
12	Goverde et al.	2000
13	Gregoriou et al.	1996
14	Guzick et al.	1999
15	Ho et al.	1989
16	Ho et al.	1992
17	Hughes et al.	2004
18	Janko et al.	1998
19	Jaroudi et al.	1998
20	Karlstrom et al.	1993
21	Kerin et al.	1984
22	Kerin et al.	1987
23	Kirby et al.	1991
24	Martinez et al.	1990
25	Melis et al.	1995
26	Murdoch et al.	1991
27	Nan et al.	1994
28	Soliman et al.	1993
29	Steures et al.	2006
30	Steures et al.	2007
31	Steures et al.	2007
32	Te Velde et al.	1989

Study characteristics

The characteristics of the included studies are summarised in Table 2. The studies varied in inclusion criteria, duration of the interventions, controlled ovarian stimulation protocols, starting dose and criteria for cancellation of insemination. The controlled ovarian stimulation protocols and the number of embryos transferred varied in the different IVF arms. Six studies registered live births per couple (Bhattacharya *et al.*, 2008;Goverde *et al.*, 2000;Guzick et al., 1999;Hughes *et al.*, 2004;Steures *et al.*, 2006;Steures *et al.*, 2007a), whereas the other two studies only reported ongoing pregnancy (Custers *et al.*, 2011;Steures *et al.*, 2007b). All studies registered multiple births, which ranged from 0% to 100%.

One study compared IUI with and without COS with ICI with or without COS. ICI was considered as a surrogate for intercourse or EM in this study (Guzick *et al.*, 1999).

Some of the data on two studies could not be included: in one study 101 couples had received other treatments (COS or IUI) before randomisation; these couples were excluded from the analysis (Hughes *et al.*, 2004). In another study couples started with three cycles of IUI without COS. If those three cycles failed, subsequent IUI cycles were performed with COS (Steures *et al.*, 2007b). We only included the first three cycles of IUI without COS reported in this study.

Assessment of study quality

The methodological quality of included studies is summarized in the last column of Table 2. Of the eight included studies (Guzick *et al.*, 1999), all had performed a power calculation. All reported adequate methods of randomization and concealment of allocation. All studies had a parallel design and all studies except one (Goverde *et al.*, 2000) were multicentre studies. In all studies the randomised groups were comparable at baseline and had a follow-up of at least 80%. Comparison of the data received from authors with the published results revealed only minimal differences in duration of subfertility, which were ignored. The quality of the data received was considered satisfactory for all included studies. There were no missing data.

Tabel 2. Study characteristics. * The chance of natural conception within 12 months, ** Couples who received treatment of IUI with or without clomifene or FSH before randomisation were excluded for this IPD, *** The post coital test **** The stimulated cycles are not included in this IPD analysis

Study	Population Inclusion criteria	Intervention	Outcome	Features of Method Quality
Bhattacharya et al. 2008 **n= 193 vs. 193 vs. 194**	Couples with unexplained or male subfertility or mild endometriosis with at least two years of infertility Female age: no age limit Basic fertility work up: confirmed ovulation and bilateral tubal patency Semen: minimum motility of 20%	Expectant management IUI without COH, Timed intercourse with COH, starting dose: 50 mg CC/day Cancel criteria: ≥3 follicles in 1st cycle Duration 6 months	Live birth Expectant management 17%, IUI without COH 14%, Timed intercourse with COH 23% Multiple birth Expectant management 1%, IUI without COH 0.5%, Timed intercourse with COH 0.5%	Power calculation: yes Randomisation telephone randomisation system Trial design: parallel Multicentre: 5 centres ITT- analysis: yes Three arms comparable at baseline: yes Follow up >80%: yes
Custers et al. 2011 **n= 58 vs. 58**	Couples with unexplained or male subfertility and a unfavourable prognosis of natural conception (≤30% according model of Hunault*) Female age: ≤37 years Basic fertility work up: confirmed ovulation and no or one sided tubal occlusion Semen: Total Motility Count of ≥3*10^6	IUI with COH, mean dose 75 IU FSH/ day (range 37-150) Cancel: 3 follicles ≥16mm, or 5 follicles ≥12 mm IVF- eSET, starting dose 100-150 IU/day FSH with GnRH agonist. ET: elective Single Embryo transfer in case of good quality embryo's Duration 4 months	Live birth IUI with COH 21% IVF eSET 22% Multiple birth IUI with COH 25% IVF eSET 14%	Power calculation: yes Randomisation computer generated randomisation Trial design: Parallel Multi centre ITT- analysis: yes Two arms comparable at baseline: yes Follow up >80%: yes

Study	Population Inclusion criteria	Intervention	Outcome	Features of Method Quality
Goverde et al. 2000 **n = 86 vs. 85 vs. 87**	Unexplained for at least 3 years or male subfertility for at least 1 year (including couples with stage I or II treated endometriosis Female age: 18-38 year Basic fertility work up: confirmed ovulation and no or one sided tubal occlusion Semen: > 20 million progressively motile spermatozoa in ejaculate in unexplained subfertility, in male subfertility < 20 million progressively motile spermatozoa in ejaculate and ≥ 600.000 progessively motile spermatozoa after Percoll processing	IUI without COHTiming IUI: 20-30 hr after LH surge IUI with COH, starting dose 75 IU/day FSH Cancel criteria:>3 follicles of ≥18 mm or > 6 follicles of ≥14 mm IVF, starting dose 150-225 IU/day FSH with GnRH agonist ET: 48-72 hr after retrieval, 2-3 embryo's Duration 6 cycles (max)	Live birth IUI without COH 29% IUI with COH 36% IVF 28% Multiple birth IUI without COH 4% IUI with COH 29% IVF 21%	Power calculation: yes Randomisation computer generated randomisation schedule in sealed envelopes Trial design: Parallel Single centre ITT- analysis: yes Three arms comparable at baseline: yes Follow up >80%: yes

Study	Population Inclusion criteria	Intervention	Outcome	Features of Method Quality
Guzick et al. 1999 **n= 233 vs. 234 vs. 234 vs. 231**	Unexplained or male subfertility and couples with stage I or II treated endometriosis Female age: ≤40 years Basic fertility work up: regular cycle normal uterine cavity and pelvis Semen: any motile sperm	ICI without COH Timing: Day after urinary LH- surge IUI without COH Timing: Day after urinary LH- surge ICI + COH, starting dose 150 IU FSH/day, cancel: E2 > 3000pg/ml IUI + COH, starting dose 150 IU FSH/day, cancel: E2 > 3000pg/ml Duration 4 cycles (max)	Live birth ICI without COH 8% IUI without COH 13% ICI with COH 15% IUI with COH 22% Multiple birth ICI without COH 6% IUI without COH 3% ICI with COH 23% IUI with COH 30%	Power calculation: no Randomisation computer generated permuted block in locked files Trial design: Parallel Multi centre, 10 clinics ITT- analysis: not possible Four arms comparable at baseline: yes Follow up >80%: yes
Hughes et al. 2004 **n= 20 vs. 18**	Couples with unexplained or male subfertility or with mild endometriosis and with at least two years of infertility Female age: 18-39 years Basic fertility work up: confirmed ovulation and no or one sided tubal occlusion Semen: adequate to perform ICSI	Expectant management (EM) ** IVF, starting dose 150-225 IU/day FSH with GnRH agonist ET: mean number of embryo's transferred: 2 and maximum 4 Duration 3 months	Live birth Expectant management 1% IVF 22% Multiple birth Expectant management 100% IVF 25%	Power calculation: yes Randomisation opaque sealed envelopes Trial design: parallel Multi centre ITT- analysis: yes Two arms comparable at baseline: yes Follow up >80%: yes

Study	Population Inclusion criteria	Intervention	Outcome	Features of Method Quality
Steures et al. 2006 **n = 127 vs. 126**	Unexplained subfertility and an intermediate prognosis (30-40%*) Female age: ≤37 years Basic fertility work up: confirmed ovulation and no or one sided tubal occlusion Semen: normal	Expectant management IUI with COH, mean dose 75 IU FSH/ day (range 37-150) Cancel: 3 follicles ≥16mm, or 5 follicles ≥12 mm Duration 6 months	Live birth: Expectant management: 24% IUI with COH: 21% Multiple birth Expectant management: 3% IUI with COH: 7%	Power calculation: yes Randomisation computer generated in balanced blocks, sealed envelopes Trial design: Parallel Multi centre, 26 centres ITT- analysis: yes Two arms comparable at baseline: yes Follow up >80%: yes
Steures et al. 2007 **n =136 vs. 136**	Abnormal PCT due to cervical factor or male factor and a poor prognosis (≤30%*) Female age: no age limit Basic fertility work up: confirmed ovulation and no or one sided tubal occlusion and a negative PCT *** Semen: normal or mild male factor	IUI without COH Timing: 20-30 hr after LH-surge or 36-40 hr after hCG IUI with COH, mean 75 IU FSH/ day (range 37-150) Cancel: 3 follicles ≥ 16mm, or 5 follicles ≥ 12 mm Duration: max 3 cycles	Live birth IUI without COH 17% IUI with COH 21% Multiple birth IUI without COH 5% IUI with COH 7%	Power calculation: yes Randomisation computer generated in balanced blocks, sealed envelopes Trial design: Parallel Multi centre, 24 centres ITT- analysis: yes Two arms comparable at baseline: yes Follow up >80%: yes
Steures et al. 2007 **n=52 vs. 49**	Couples with an isolated cervical factor and a good prognosis (≥30%*) Female age: no age limit Basic fertility work up normal, semen normal or one sided tubal occlusion and a negative PCT *** Semen: normal	IUI without COH Timing: 20-30 hr after LH-surge or 36-40 hr after hCG After 3 failed cycles, IUI with COH was given**** Expectant management Duration 3 months	Live birth: Expectant management: 19% IUI without COH: 31% Multiple pregnancies: Expectant management: 0% IUI without COH: 6%	Power calculation: yes Randomisation computer generated in balanced blocks, sealed envelopes Trial design: Parallel Multi centre, 17 centres ITT- analysis: yes Two arms comparable at baseline: yes Follow up >80%: yes

Table 3. The prognosis according the prognostic model of Hunault, the chance of natural conception within 12 months according the prognostic model of Hunault et al. (2004)

Study	Mean prognosis according the model of Hunault (SD)	
Bhattacharya 2008	Expectant management	30.1% (9.4)
	IUI	30.3% (10.1)
	Timed intercourse with COH	29.5% (9.4)
Custers 2011	IUI-COS	20.8% (6.8)
	IVF eSET	20.7% (5.4)
Goverde 2000	IUI without COS	25.5% (10.2)
	IUI-COS	24.4% (10.8)
	IVF	24.2% (12.0)
Guzick 1990	ICI without COS	29.6% (13.3)
	IUI without COS	28.2% (12.7)
	ICI- COS	29.9% (12.6)
	IUI- COS	29.5% (12.4)
Hughes 2004	Expectant management	22.7% (13.9)
	IVF	24.1% (10.6)
Steures 2006	Expectant management	28.7 % (6.0)
	IUI- COS	28.6 % (5.3)
Steures 2007	IUI without COS	23.4% (6.9)
	IUI-COS	24.1% (6.2)
Steures 2007	Expectant management	39.3 % (8.5)
	IUI without COS	37.0% (8.2)

Interaction between prognosis and efficacy of treatment

The chance of a natural conception within 12 months was calculated for all included couples based on the variables in the datasets (Hunault *et al.*, 2004). For the variables female age, duration of subfertility, subfertility being primary or secondary and sperm motility, there were no missing data. In four studies (Bhattacharya *et al.*, 2008;Goverde *et al.*, 2000;Guzick *et al.*, 1999;Hughes *et al.*, 2004) the datasets did not include a variable concerning the referral status (secondary or tertiary care), but based on the context of the publication or after contacting the author, we categorized all couples in these four studies as secondary care patients. The prognosis of natural conception is summarized in Table 3. The mean prognosis was comparable between treatment arms in the included trials and the standard deviation of prognosis varied from 5.3 and 13.9%.

The intercepts, slopes and interaction terms for the treatment strategies in each study are shown in Table 4. To facilitate interpretation, we have integrated the treatment term in the intercepts, and the interaction term in the slope. Differences in the overall treatment effect would then become apparent as a difference in the intercept; differences in the effect of prognosis would show themselves as a difference in slope. The far right column in Table 4 shows the p-value to indicate differences in slopes: the interaction between treatment and prognosis. The interaction term was not statistically significant in any of the trials, indicating that there was no evidence of a significant differential effect of prognosis on the efficacy of treatment.

Table 4. Intercepts, slopes and interaction terms of the treatment strategies per study

Study	Treatment arms	Intercept (CI) Treatment Effect	Slope (CI) Prognosis Effect	p-value Interaction prognosis* treatment
Bhattacharya 2008 **n = 580**	Expectant management IUI without ovarian stimulation TI with ovarian stimulation	-2.30 (-3.56; -1.04) -1.42 (-2.50; -0.34) -2.25 (-3.55; -0.92)	0.023 (-0.021; 0.071) 0.006 (-0.342; 0.341) 0.017 (-0.025; 0.059)	ref 0.711 0.694
Custers **2011** **n = 116**	IUI with ovarian stimulation IVF	-3.08 (-5.22; -0.94) -1.43 (-3.87; 1.03)	0.084 (-0.006; 0.174) 0.009 (-0.105; 0.123)	ref 0.312
Goverde **2000** **n = 258**	IUI without ovarian stimulation IUI with ovarian stimulation IVF	-1.78 (-2.99; -0.57) -0.50 (-1.64; 1.19) -0.42 (-1.45; 0.61)	0.043 (0.003; 0.083) 0.006 (-0.033; 0.045) 0.010 (-0.025; 0.045)	ref 0.190 0.219
Guzick **1990** **n = 932**	ICI without ovarian stimulation IUI without ovarian stimulation ICI with ovarian stimulation IUI with ovarian stimulation	-3.28 (-4.55; -2.01) -2.57 (-3.55; -1.57) -2.82 (-3.86; -1.79) -2.27 (-3.23; -1.31)	0.026 (-0.009; 0.061) 0.022 (-0.007; 0.051) 0.035 (0.006; 0.064) 0.032 (0.006; 0.058)	ref 0.671 0.878 0.776
Steures **2006** **n = 253**	Expectant management IUI with ovarian stimulation	-1.84 (-3.82; 0.15) -3.00 (-5.31; -0.69)	0.023 (-0.043; 0.090) 0.057 (-0.019; 0.133)	ref 0.517
Steures **2007** **n = 272**	IUI without ovarian stimulation IUI with ovarian stimulation	-1.696 (-3.32; -0.09) -2.475 (-4.14; -0.79)	0.003 (-0.063; 0.669) 0.045 (-0.021; 0.112)	ref 0.675
Steures **2007** **n = 101**	Expectant management IUI without ovarian stimulation	-1.274 (-4.83; 2.29) -2.775 (-5.78; 0.23)	0.012 (-0.076; 0.100) 0.048 (-0.028; 0.124)	ref 0.382

Prognosis by treatment curves

The prognosis-by-treatment curves are shown in Figure 2a-g. To facilitate interpretation of the curves we discuss four studies in more detail. The curve for the trial of Bhattacharya *et al*. (2008) is shown in Figure 2a. Most couples had a probability between 20% and 30% of conceiving naturally within 12 months. With all three treatment strategies the probability of live birth increased with a better prognosis of natural conception. In couples with a poor prognosis of natural conception the probability of live birth was higher for those treated with IUI without COS compared to EM and timed intercourse with clomiphene citrate. In couples with a prognosis of natural conception of more than 50%, the probability of live birth was higher in couples who received EM. In couples receiving only clomiphene citrate (CC) the probability of live birth was lower in all couples, regardless of prognosis. The slopes of all three lines in the curve differ, but as shown in Table 4, this difference did not reach statistical significance (interaction IUI and EM p= 0.711 and interaction CC and EM p=0.694).

In the study of Custers *et al*. (2011) (Figure 2b) the probability of ongoing pregnancy also seems to differ between the two treatment strategies. The curve shows a higher probability of ongoing pregnancy in couples with a poor prognosis of natural conception when treated with IVF. In couples with a good prognosis of natural conception the probability of ongoing pregnancy was higher if they received IUI with COS. This difference in slope did not reach statistical significance (p= 0.312, Table 4).

The prognosis-by-treatment curves of the study of Goverde *et al*. (2000) (Figure 2c) shows that in couples with a poor prognosis the probability of live birth is higher in couples treated with IUI with COS and IVF compared to couples treated with IUI without COS. In couples with a good prognosis the predicted probability of live birth is higher in couples who received IUI without COS. This difference in slope did not reach statistical significance (p= 0.190 and 0.219, Table 4).

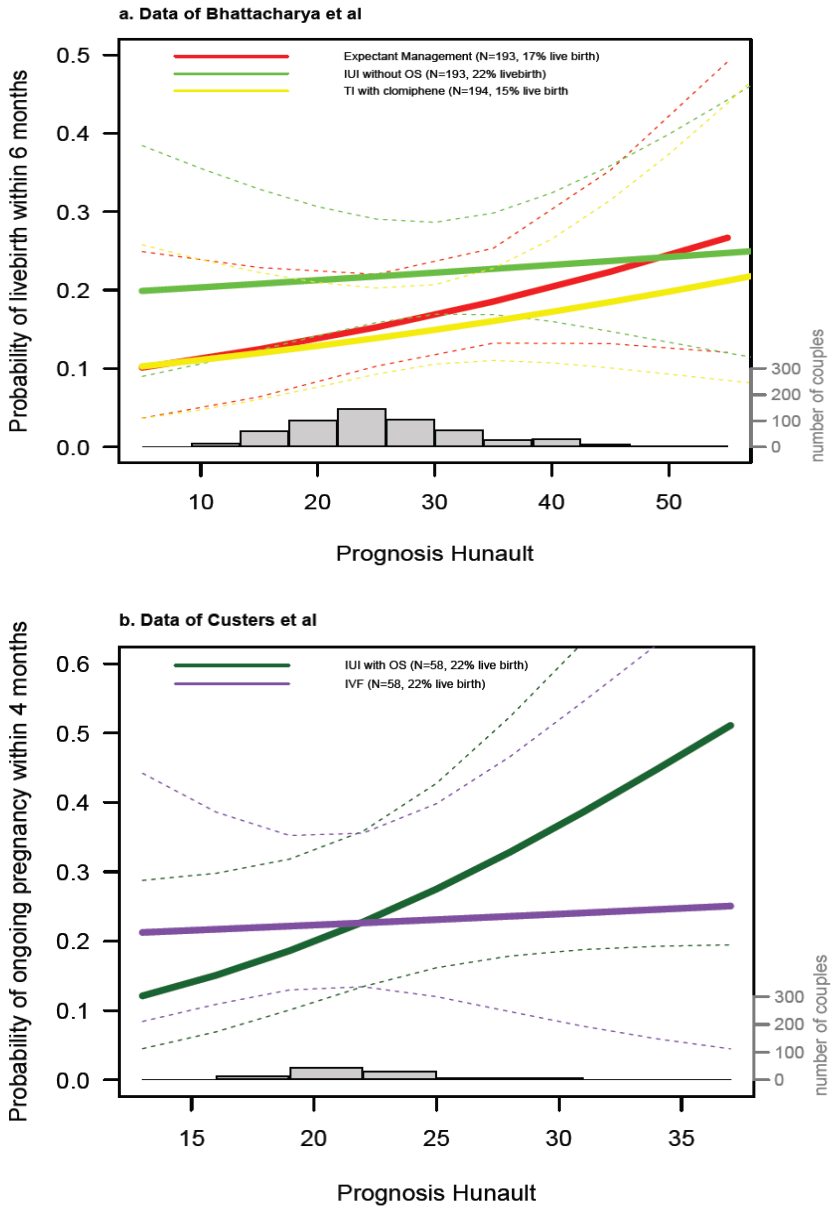
In the study of Guzick *et al*. (1999) ICI in a natural cycle (n=233) and in a stimulated cycle (n=234) were compared with IUI in a natural cycle (n=234) and in a stimulated cycle (n=231), in couples with unexplained subfertility or male subfertility. The prognosis-by-treatment curves (Figure 2d) show a higher predicted probability of live birth in all couples treated with IUI or ICI with COS. In this study prognosis does not help in differentiating between treatment options. All interaction terms between prognosis and treatment in this study were not significant (p= 0.617, p= 0.878, p= 0.776, Table 4).

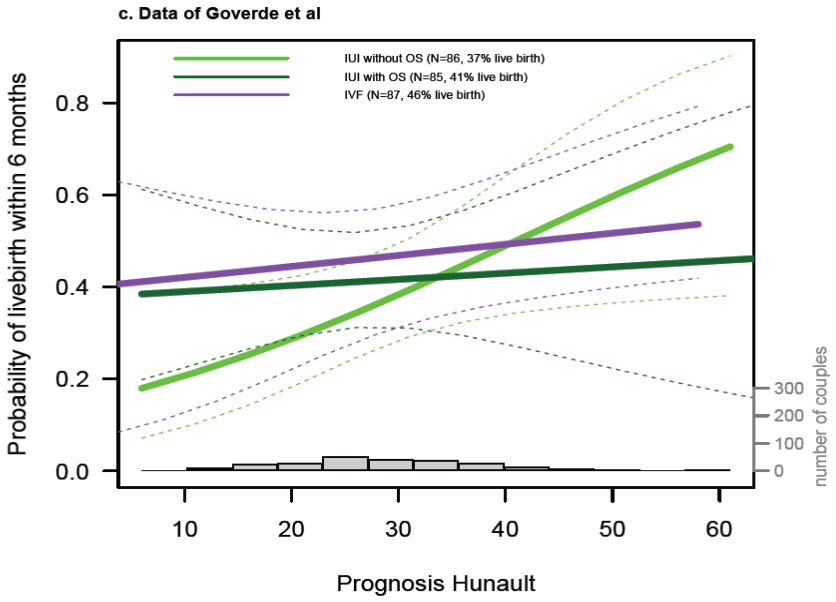
The trends of the curves of the two other studies can be observed in Figure 2e-f. We did not plot curves for the study of Hughes *et al*. (2004) which compared IVF (n= 18) with EM (n= 20) because after excluding the couples who received treatment before randomisation, the number of included couples was too small to draw a reliable curve.

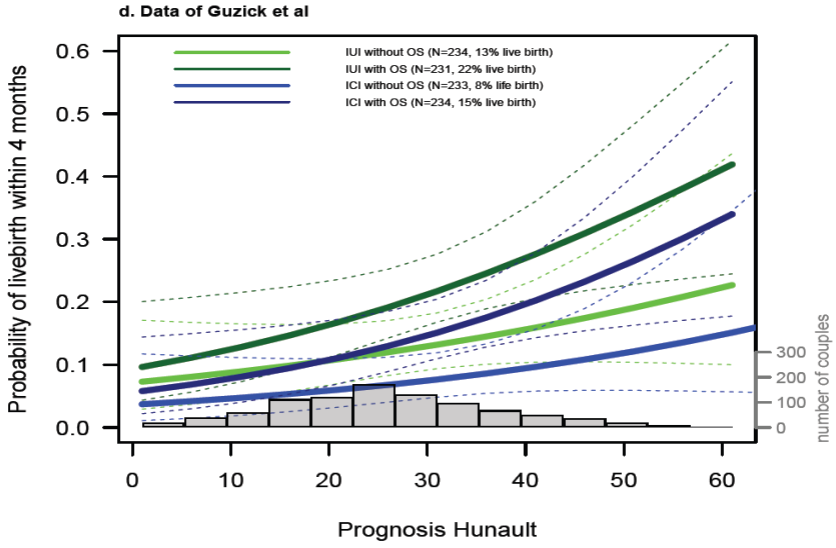
To compare the prognostic marker female age with the Hunault score on the effectiveness of assisted conception we also plotted female age-by-treatment curves for all studies (data not shown). Age appeared to be a poorer predictor than the Hunault score.

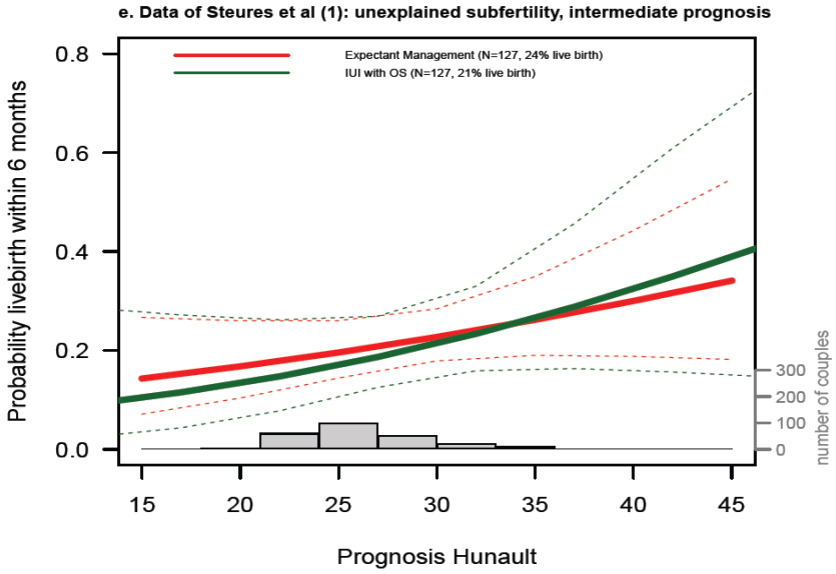
The heterogeneity in treatment protocols precluded the use of meta-analysis and the benefits of increased precision from pooling data.

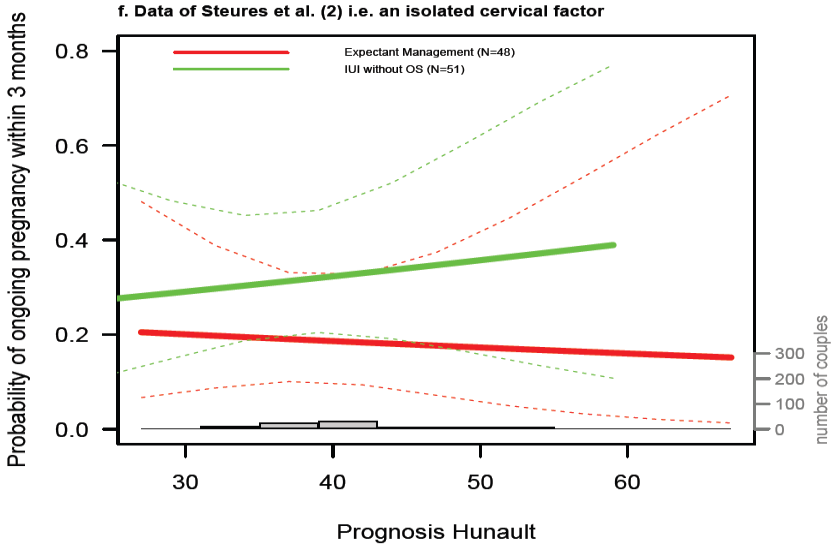
Figure 2: Predictiveness curves of different treament strategies

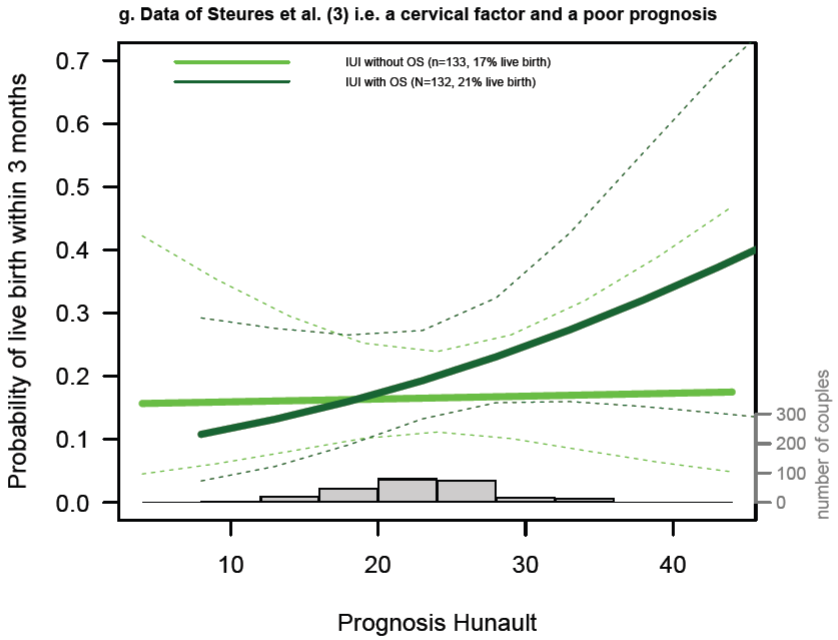



c. Data of Goverde et al
IUI without OS (N=86, 37% live birth)
IUI with OS (N=85, 41% live birth)
IVF (N=87, 46% live birth)
Probability of livebirth within 6 months
0.0
0.2
0.4
0.6
0.8
10
20
30
40
50
60
Prognosis Hunault
number of couples
0
100
200
300


d. Data of Guzick et al
IUI without OS (N=234, 13% live birth)
IUI with OS (N=231, 22% live birth)
ICI without OS (N=233, 8% life birth)
ICI with OS (N=234, 15% live birth)
Probability of livebirth within 4 months
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0
10
20
30
40
50
60
Prognosis Hunault
number of couples
0
100
200
300


e. Data of Steures et al (1): unexplained subfertility, intermediate prognosis
Expectant Management (N=127, 24% live birth)
IUI with OS (N=127, 21% live birth)
Probability livebirth within 6 months
0.0
0.2
0.4
0.6
0.8
15
20
25
30
35
40
45
Prognosis Hunault
number of couples
0
100
200
300


f. Data of Steures et al. (2) i.e. an isolated cervical factor
Expectant Management (N=48)
IUI without OS (N=51)
Probability of ongoing pregnancy within 3 months
0.0
0.2
0.4
0.6
0.8
30
40
50
60
Prognosis Hunault
number of couples
0
100
200
300



DISCUSSION

Currently, there is no consensus on the best treatment strategy for couples with unexplained or mild male subfertility. In this study we explored the possibility of using prognosis of natural conception to select the best treatment strategy for these couples. We collected data from 8 primary studies including 2,550 couples, almost 60% of all treatment-naïve couples ever randomised between EM, IUI or IVF and published. Our results showed that the probability of live birth or ongoing pregnancy tended to be higher with a better prognosis of natural conception but we were unable to confirm a statistically significant differential effect of prognosis of natural conception on treatment efficacy.

A major strength of this study is that we were able to collect data for almost 60% of all couples ever randomised in studies evaluating the efficacy of EM, TI, ICI or IUI with or without COS and IVF in couples without a major cause for their unfulfilled child wish. Authors of 12 studies did not have their data anymore and authors of another 12 studies could not be traced: overall these studies were older, which explains why it was harder to trace the data or the author. Untraceable studies were relatively small and the majority of these studies had a cross-over design. The studies that we included in this IPD analysis were the largest ones, the most recent ones and also those of high quality.

The importance of patient selection based on prognosis of natural conception has been stressed before and validated prognostic models estimating the chances of treatment

independent, i.e. natural conception are available (Collins *et al.*, 1983;Leushuis *et al.*, 2009). In an impact study of the prognostic model of Hunault, couples with an intermediate prognosis were randomly allocated to EM or IUI with COS, both for six months. The live birth rates in both groups were comparable, suggesting couples with an intermediate or a poor prognosis are better off with EM Steures *et al.* 2006). The present study aimed to confirm an association between prognostic profiles and the efficacy of assisted conception, but failed to find a significant effect of prognosis on treatment outcome.

One explanation for our negative findings may be differences in stimulation protocol and embryo transfer policies between the included studies which may override the impact of patient profile. Especially in the treatment arms of IUI with COS, higher dosage of controlled ovarian stimulation and milder cancellation criteria are not only associated with higher pregnancy rates but also higher risks of multiple pregnancies. For example, treatment of IUI with COS for 6 cycles resulted in one study in a live birth of 36% and multiple birth rate of 29% (Goverde *et al.*, 2000) compared to the same treatment for 6 months in another study with a live birth rate of 21% and a multiple pregnancy rate of 7% (Steures *et al.*, 2006). At the moment most countries find multiple birth rates of 29% not acceptable (ESHRE position paper, 2008), as multiple births are associated with higher morbidity and mortality rates for both mother and child compared to singleton pregnancies (Gerris *et al.*, 2005; Helmerhorst *et al.*, 2004). This high multiple birth rate reduces the applicability of the results of our study and also of the original study (Guzick *et al*., 1999): unfortunately this is the largest RCT performed in this field (n=932). This issue emphasizes the need for more large RCTs evaluating the efficacy of IUI and IVF for couples with unexplained or male subfertility.

Our results indicate that the effect rate of IUI COS is largely correlated with twin rates. Our results question the impact of prognostic profile on the efficacy of IUI COS, implicating that the treatment effect is also limited in poor prognosis couples. Consequently, acceptable pregnancy rates in these couples are only achieved through a high multiple pregnancy rate. We should keep in mind here that studies reported on, at maximum, 6 cycles whereas many couples with unexplained subfertility will have 5 to 10 years of reproductive chances ahead, corresponding to 60 - 120 cycles. Thus, the contribution of these IUI COS cycles on the overall reproductive outcome might be rather limited and should be considered with care, specifically when high multiple pregnancy rates occur.

Only three studies in this IPD analysis included IVF, of which one was relatively small (Hughes *et al.*, 2004) , one used IVF elective single embryo transfer (Custers *et al.*, 2011) and one was relatively old (Goverde *et al.*, 2000). As a consequence, no firm conclusions can be drawn regarding the relation between prognosis and treatment outcome after IVF. Nevertheless, these are the only data available on treatment-naïve couples ever randomised between assisted conception or EM (Pandian *et al*., 2012). Only one relatively old study that compared IVF with EM did not supply data because the data were no longer available (Soliman *et al.*,

1993). The fact that all the data on IVF cycles performed within clinical trials are, in one way or another, of relatively poor quality stresses the need for RCTs studying IVF.

CONCLUSION

Although we did observe a trend in the prognosis-by-treatment curves towards a relation between the chances of natural conception and the outcome of treatment, we did not find a significant effect of prognosis on treatment outcome. The included studies in themselves are too small to detect any differential capacity of the prognostic models on treatment outcome. The heterogeneity in treatment protocols precluded the use of meta-analysis and the benefits of increased precision from pooling data. Additional data from larger trials are needed to evaluate the existence of a differential effect of prognosis on treatment outcome with greater precision.

Authors' roles

BM is the principal investigator of this study. NB and AB are responsible for the literature search and NB is responsible for the overall logistical aspects of this study, drafted the first version of this paper and performed the analysis together with KO, PB, BM, FvdV, and PH. SB, IC, AJG, DG, PS, EH shared their data and all authors read and approved the final paper.

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Conflict of interest

In this study no conflicting interests are involved.

Exclusive licence

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors.

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Chapter 9

General Discussion

The effectiveness of more than 50% of all interventions in medicine is unknown (BMJ Evidence Centre 2011). As Donald Rumsfeld, the former American minister of Defence, mentioned in 2002, it is important to distinguish the known unknowns from the unknown unknowns (Donald Rumsfeld 2002). The extent of the latter is unclear, but critical judgement of available evidence can create awareness of the unknown unknowns and move them to the category known unknown. It is then possible to evaluate them according to the principles of evidence-based medicine and transfer them to the category of known knowns.

We have also rather recently become aware that this process does not end when a known unknown has become a known known, because the known knowns summarized in clinical guidelines, do not implement themselves. Literature from several countries suggest that approximately 30-40% of patients still do not receive care based on the best available evidence and 20-25% of provided health care is considered unnecessary or potentially harmful (Grol 2001; McGlynn et al. 2003; Schuster et al. 1998).

In reproductive medicine the evidence concerning the effectiveness of fertility treatments in couples without a major cause for their unfulfilled child wish is inconclusive (Bensdorp et al. 2007; Steures et al. 2008; Verhulst et al. 2006; Veltman-Verhulst et al. 2012) . In these cases, prognostic models can help to predict the chance of treatment (in)dependent pregnancy for the individual couple (Leushuis et al. 2009). For instance, an impact analysis of a prognostic model predicting the chance of natural conception showed that in couples with an intermediate or high chance of natural conception, intra uterine insemination with ovarian stimulation had no beneficial effect on livebirth rate compared to expectant management (Steures et al. 2006). Based on this impact analysis our national guideline concerning subfertility recommends an expectant management for 6-12 months in couples with a favourable prognosis (NVOG: national guideline subfertility 2011). We call this strategy, i.e. an expectant management in subfertile couples with a good/intermediate prognosis of natural conception, tailored expectant management (TEM). Optimal adherence to TEM can lead to the prevention of unnecessary treatment, complications, physical and psychological burden and costs.

To what extent these prognostic models can be used to select couples for IUI or IVF is unclear. In this thesis we tried to contribute to optimal implementation of TEM and the role of prognostic models in treatment selection, in two ways.

Firstly we assessed how tailored expectant management is implemented in daily Dutch practice. In a prospective cohort study we found a moderate adherence to TEM and this adherence decreased when the woman is older and the duration of the subfertility is longer. The presence of a fertility doctor in a clinic may prevent early treatment **(chapter 2)**. Potential weakness of this cohort study is that we measured the adherence to a study protocol instead of the adherence to an (inter-) national guideline. At the time of this study the subfertility guideline was not so explicit in advice for TEM. As the recruiting doctors in this study cohort were probably more dedicated compared with an ‘average doctor’, we hypothesize that

early treatment in daily practice must be even higher, as has been demonstrated previously (Mourad et al., 2008).
Professionals' and patients' barriers and facilitators for tailored expectant management were evaluated qualitatively and quantitatively. Multivariate analyses were performed to evaluate which factors predict patients' appreciation of TEM and professionals' adherence to TEM. Based on these studies we conclude that the implementation of tailored expectant management in couples with a good prognosis can be enhanced by developing adequate patient information material, implementing regular fertility meetings where patients are discussed after the fertility work-up, implementing local protocols and by improving the knowledge of doctors about prognostic models and their communication skills with interactive training sessions **(chapters 3 and 4)**.
An implementation strategy focussing on these findings was developed and will be tested in a cluster randomised trial. In this trial, clinics and their allied general practitioner units are randomised between the multifaceted implementation strategy versus usual care. According the new guideline, the general practitioner can also perform a fertility work-up, calculate a prognosis for the couple and in case of a good prognosis advice TEM. The prognosis can be calculated with the validated model of Hunault with or without the post-coital test (Hunault et al. 2004). The effect of the strategy will be evaluated by a pre- and post-randomisation data collection and a process and economic evaluation. The study protocol of this cluster randomised trial is described in **chapter 5**.

In addition to the implementation study we aimed in the second part of this thesis to evaluate the applicability of prognosis of natural conception. This evaluation was twofold. Firstly, we compared two methods for fertility treatment selection: a funding based selection strategy used in New Zealand and a selection strategy based on the validated prognostic model of Hunault. In a cohort of 663 couples we found a fair agreement between the two treatment selection methods, a comparable discrimination and a better calibration in the selection method with the validated prognostic model of Hunault **(chapter 6)**.

Secondly, we evaluated to what extent prognostic models can help to select subfertile couples for IUI or IVF. To accomplish this, we gathered data of published randomised controlled trials in which treatments options for these couples were compared. We managed to collect data of almost 60% of all treatment naïve couples, ever randomised between expectant management, IUI or IVF. After analysing these data of 2551 randomised couples, we found no significant differential effect of prognosis on treatment outcome. Between the studies the same treatment arms followed different treatment protocols which made it impossible to merge the data in a meta-analysis. However, a non-significant trend was observed that couples with a high chance of natural conception are better off with less invasive treatment strategies like expectant management or IUI in a natural cycle and vice versa **(chapter 7 and 8)**.

At this moment, the management of couples with unexplained subfertility is empirical and many different regimens are used. Among these various treatment options are expectant management, intrauterine insemination with or without ovarian stimulation and IVF. There is no definitive evidence to show that any treatment is better than the other.
In this thesis we showed that at the moment evidence for prognosis of natural conception as a treatment selection marker for couples with unexplained subfertility is not available. There is a need for large randomized controlled trials to identify the best treatment option in couples with unexplained infertility. It is important to include prognostic factors in such trials so we can determine the effect of a pre-treatment calculated prognosis on treatment outcome. One ongoing multicentre randomised controlled clinical trial in the Netherlands is comparing six cycles of intra uterine insemination with controlled ovarian stimulation with six cycles of modified natural cycle IVF and three cycles with IVF-elective Single Embryo Transfer (eSET) within a time frame of 12 months. Couples with unexplained subfertility or mild male subfertility and a poor prognosis for natural conception (<30% according to the Hunault model) are included in this study. The results of this trial are expected in 2013 and it would be of interest to include these data in our individual patient data analysis on the relationship between prognosis and treatment outcome (Bensdorp et al. 2009).

As long as there is no evidence for optimal treatment we have to base our management on the best available evidence. Within this thesis the relevance of expectant management in couples likely to conceive naturally within 12 months has been stressed repeatedly. Treatments such as IUI or IVF should only be proposed to couples with a sufficiently low probability of treatment-independent pregnancy to avoid unnecessary medication and procedures and subsequent complications.
The discussion on when and how to treat couples with unexplained subfertility also brings us to the issue whether unexplained subfertility is a disease or not. If a patient with abdominal pain visits the hospital and no abnormalities are found after the diagnostic work-up, we send the patient home with the message: “There is nothing wrong, we cannot help you, good luck.” Or we may diagnose the patient with irritable bowel syndrome and give her some diet advices, but we would not give her a potential harmful therapy leading to more morbidity and mortality if there is no evidence for effectiveness of this therapy.
The question to be asked is why we do so in reproductive medicine. Is it because of pressure for treatment from the patient, have we been seduced by the pharmaceutical industry or do we exploit despair from infertile patients for our own purposes or income? In our national survey described in this thesis nobody declared to have economic arguments to refrain from TEM, but maybe the social desirable answer was given. Seventy-four percent of the professionals that participated in our survey experienced the urgency for action of the patients as a barrier for TEM.
Is it now still possible to perform a solid evaluation of IVF for couples with unexplained subfertility? The new Cochrane review concerning IVF in couples with unexplained

subfertility has come to the same conclusion as in 2005: "IVF may be more effective than IUI+SO. Due to paucity of data from RCTs the effectiveness of IVF for unexplained infertility relative to expectant management, clomiphene citrate and IUI alone remains unproven. Adverse events and the costs associated with these interventions have not been adequately assessed" (Pandian et al. 2005; Pandian et al. 2012). More studies are needed comparing IVF with expectant management in couples with unexplained subfertility and in these studies prognostic factors must be registered. The question is whether patients will participate in such trial or whether they will seek their comfort in commercial clinics in the Netherlands or abroad, if randomised to expectant management (Shenfield et al. 2010).

The time for large trials comparing IVF with expectant management taking prognosis into account is now, before the commercialisation in our medical care system makes such trials even more challenging or even impossible.

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Chapter 10

Summary in English and Dutch

SUMMARY

Tailored expectant management in reproductive medicine

Subfertility is defined as a failure to conceive after at least one year of regular unprotected intercourse. It affects approximately 10% of couples in their reproductive lives(Boivin et al. 2007; Gnoth et al. 2003). The incidence of subfertility is increasing in the developed world mainly due to postponement of maternity. After a basic fertility work up about 25% of all subfertile couples is diagnosed with unexplained subfertility, 30% with a mild male factor, 5% with a severe male factor, 20% with an ovulation disorder and in 20% of the couples other diagnoses are made.

In couples with unexplained or mild male subfertility, i.e. >50% of all subfertile couples, fertility treatments as intra uterine insemination (IUI) with or without ovarian stimulation (OS) and in vitro fertilisation (IVF) are not always leading to higher pregnancy rates than expectant management. To select couples for expectant management prognostic models that predict the chance of natural conception have been developed. One large randomised controlled trial showed that if chances of natural conception are intermediate or good, an expectant management for 6-12 months is as effective as IUI with OS. We call this strategy, i.e. expectant management in couples with good prospects of natural conception, tailored expectant management (TEM). TEM is not always practiced, leading to overtreatment, unnecessary complications and costs. A common complication of fertility treatment is a multiple pregnancy, which is associated with a higher morbidity and mortality in both mothers and neonates.

It is unclear how TEM is implemented in the Netherlands, but two large prospective cohort studies suggest a poor implementation. This thesis aimed to contribute to the implementation of TEM. To improve the implementation of TEM a systematic approach is needed including: acquiring data of current practice; identification of potential determinants; analysis of barriers and facilitators for the implementation, development of an implementation strategy and finally an evaluation of the implementation strategy. In this thesis this systematic approach was used to gain insight in the options to improve the implementation of TEM.

In addition to the implementation study we aimed in the second part of this thesis to evaluate the applicability of prognosis of natural conception. This evaluation was twofold.

Firstly, we compared two selection methods for fertility treatment: a funding based selection strategy used in New Zealand and a selection strategy based on the validated prognostic model of Hunault. In New Zealand public funding for fertility treatment is restricted to subfertile women who are unlikely to conceive naturally, based on clinical and social criteria known as the clinical priority access criteria (CPAC-score). In the Netherlands couples are selected for treatment based on their prognosis of natural conception. The performance of both selection methods were compared in a New Zealand cohort of 663 couples.

Secondly, we aimed to explore the selective capacities of the prognostic model predicting the chance of natural conception in more detail. At the moment it is unclear if prognosis can help the physician to choose the proper - i.e. most (cost-) effective- treatment for subfertile couples with unexplained or mild male subfertility. In this last part of the thesis we will evaluated if prognosis can select couples for a specific treatment. We addressed this issue by analysing individual patient data (IPD) of published randomised controlled trials. Authors of published randomised trials comparing expectant management (EM), intracervical insemination (ICI), IUI, all three with or without OS and IVF, in couples with unexplained or male subfertility were contacted and invited to share their original data. In all datasets, we calculated the chances of natural conception for each couple with the validated prognostic model. We then constructed prognosis-by-treatment curves and tested whether prognosis can help to choose the most effective treatment strategy for the individual couple.

Chapter 1 gives an outline and describes the objectives of this thesis.

Chapter 2 reports the results of a cohort study in which we assessed risk factors for non-adherence to tailored expectant management (TEM). Couples with mild male, unexplained and cervical subfertility were included in this multicentre prospective cohort study. If the probability of natural conception according to the prognostic model of Hunault within 12 months was ≥40%, the study protocol advised an expectant management for 6–12 months. Multivariable logistic regression was used to identify patient and clinical characteristics associated with non-adherence to TEM. In total 3021 couples were included in this cohort of whom 1130 (38%) had a ≥40% probability of natural conception. Follow-up was available for 1020 (90%) couples of whom 214 (21%) had started treatment between 6 and 12 months and 153 (15%) within 6 months.
A higher female age and a longer duration of subfertility were associated with treatment within 6 months (OR: 1.06, 95% CI: 1.01–1.1; OR: 1.4; 95% CI: 1.1–1.8). A fertility doctor in a clinical team reduced the risk of treatment within 6 months (OR: 0.62; 95% CI: 0.39–0.99). We concluded that in couples with a favorable prognosis of natural conception, there is considerable overtreatment, especially if the woman is older and duration of the subfertility is longer. The presence of a fertility doctor in a clinic may prevent early treatment.

In **chapter 3** we aimed to identify any barriers or facilitators for tailored expectant management among professionals and subfertile couples. A qualitative study was performed with semi structured in-depth interviews among 21 subfertile patients who were counselled for TEM. In addition, three focus-group interviews were held with 21 professionals within the field of reproductive medicine. Two theoretical models were used to guide the interviews and the analyses. The primary outcome was the set of identified barriers and facilitators which influence implementation of TEM.

Among the subfertile couples, main barriers were a lack of confidence in natural conception, a perception that expectant management is a waste of time, inappropriate expectations prior to the first consultation, misunderstanding the reason for expectant management and overestimation of the success rates of treatment. Both couples and professionals saw the lack of patient information materials as a barrier. Among the professionals, limited knowledge about prognostic models leading to a decision in favour of treatment was recognized as a main barrier. A main facilitator mentioned by the professionals was better management of patients' expectations.

Chapter 4 describes a nationwide survey to assess the prevalence of the barriers and facilitators identified in chapter 3 and to evaluate which factors predict patients' appreciation of TEM and professionals' adherence to TEM. Two questionnaires were developed based on the identified barriers and facilitators and sent to 195 couples and 167 professionals. Multivariate analysis was performed to evaluate which factors predicted patients' appreciation of TEM and professional adherence to TEM.
In total, 118 (61%) couples and 117 (70%) professionals responded and 96 couples and 117 professionals were included in the analysis. Patients' mean appreciation of TEM was 5.7, on a 10-point Likert scale. Patients with a lower appreciation of TEM had a higher need for patient information ($p = 0.047$). The professionals reported a mean adherence to TEM of 63%. Adherence to TEM was higher when professionals were fertility doctors ($p = 0.041$). Facilitators in the clinical domain were associated with a higher adherence to TEM ($p = 0.091$). Barriers in the professional domain had a negative impact on adherence to TEM ($p = 0.008$).

Chapter 5 describes the study protocol of an ongoing cluster randomized trial that tests a multifaceted implementation strategy to improve the implementation of tailored expectant management (TEM). Current implementation of TEM is not optimal (chapter 2). Based on the barriers and facilitators of TEM that were identified among professionals and subfertile couples in chapter 3 and 4, we developed a multifaceted implementation strategy. This implementation strategy focuses on infertile couples and their care providers i.e. general practitioners (GPs), fertility doctors and gynecologists. The implementation strategy addresses three levels: (1) Patient level: education materials in the form of a patient information leaflet and a website; (2) Professional level: audit and feedback, educational outreach visit, communication training and access to a digital version of the prognostic model of Hunault on a website; (3) Organizational level: providing a protocol based on the guideline. In a cluster randomized trial, 25 clinics and their allied practitioners units are randomized between the multifaceted implementation strategy and care as usual. The effect of the implementation strategy, i.e. the percentage guideline adherence on TEM, will be evaluated by pre- and post-randomization data collection. Furthermore there will be a process and cost evaluation of the strategy.

Chapter 6 describes a study on the performance and measure of agreement of two fertility treatment selection methods: the CPAC score and the prognostic model of Hunault. In New Zealand public funding for fertility treatment is restricted to subfertile women who are unlikely to conceive naturally, based on clinical and social criteria known as the clinical priority access criteria (CPAC-score). In this study this CPAC score was compared with the prognostic model developed in the Netherlands (the Hunault model).
For this comparison a New Zealand (NZ) cohort of 663 couples with unexplained subfertility was used. Of the 663 couples referred, 249 (38%) couples had unexplained subfertility. Of 246 women with follow-up data, there were 143 (58%) who had a live birth or ongoing pregnancy during the follow up period of 4-5 years, 65 (26%) after fertility treatment and 78 (32%) after natural conception.
There were 100 couples (41%) who had a Hunault prediction score of < 30%, which is the treatment threshold according the Dutch National Fertility guidelines and 36 (15%) couples who had a CPAC score of >65, which is the New Zealand threshold for publically funded treatment. There were 69 couples (28%) who met the threshold for treatment in the Netherlands, but did not meet the New Zealand threshold for public funding. The kappa coefficient as a measure of agreement of the two scores and their treatment thresholds was 0.30 suggesting a fair agreement. The discriminative capacity was comparable between the two selection methods (AUC: 0.63), but the Hunault model performed better in calibration.
In **chapter 7** the study protocol of an individual patient data (IPD) analysis of the relation between the prognostic profile of subfertile couples and treatment outcome after EM, IUI and IVF is described. Most studies that evaluated the effectiveness of these treatment options have not taken the couples' prognosis into account, which may or may not influence the effect of treatment. Individual patient data analyses allow us to take these prognostic factors into account, and to evaluate their effect on treatment outcome. This study aimed to use anonymised data from relevant published trials to perform an individual patient data meta-analysis, evaluating the effect of couples' prognosis on the effectiveness of EM, IUI, with or without COS, and IVF. Based on earlier systematic reviews and an updated search, randomised controlled trials were considered for inclusion. Authors of the included studies were invited to share their original anonymised data. The data were assessed on validity, quality and completeness. The prognosis of the individual couple was calculated and its' effect on treatment outcome analysed.

Chapter 8 reports the results of the study protocol described in chapter 7. We acquired data from 8 RCTs, including 2,550 couples. In three studies the more invasive treatment strategies appeared less effective in couples with a high chance of natural conception, but this difference did not reach statistical significance (p-value for interaction 0.71, 0.31 and 0.19). In one study the strategies with OS (IUI and ICI) led to higher pregnancy rates than unstimulated strategies, regardless of prognosis, but at the expense of a high twin rate. In two studies, the more invasive treatments strategies appeared more effective in couples

with a good prognosis, but this difference did not reach statistical significance (p-value for interaction 0.38 and 0.68 respectively). In one study, prognosis was already incorporated in the inclusion criteria and its' differential effect on treatment effect was limited. The only study that compared EM with IVF included 38 couples, and was too small for a precise estimate. Our analyses exclude large differential effects of prognosis on effectiveness of fertility treatment.

SAMENVATTING

Afwachtend beleid bij subfertiele paren met een goede kans op natuurlijke conceptie

Een paar is subfertiel als er na een jaar onbeschermde geslachtsgemeenschap geen zwangerschap optreedt. Naar schatting wordt 10% van alle paren met een kinderwens hiermee geconfronteerd. De incidentie van subfertiliteit neemt toe in de ontwikkelde wereld, voornamelijk als gevolg van de toenemende leeftijd waarop de vrouw de keuze maakt voor het moederschap. Na een oriënterend fertiliteitsonderzoek wordt ongeveer 25% van alle subfertiele paren gediagnosticeerd met onverklaarde subfertiliteit, 30% met een milde mannelijke factor, 5% met een ernstige mannelijke factor, 20% met een ovulatiestoornis en in 20% van de paren wordt een andere diagnose gesteld. Bij paren met onverklaarde of milde mannelijke subfertiliteit die meer dan 50% van alle subfertiele paren uitmaken, leiden vruchtbaarheidsbehandelingen zoals intra-uteriene inseminatie (IUI) met of zonder ovariële stimulatie (OS) en in vitro fertilisatie (IVF) niet altijd tot betere zwangerschapscijfers dan een afwachtend beleid. Om de juiste koppels voor een afwachtend beleid te selecteren zijn prognostische modellen ontwikkeld die de kans op natuurlijke conceptie kunnen voorspellen. In een groot gerandomiseerd onderzoek bleek dat bij paren met een gemiddelde zwangerschapskans een afwachtend beleid van 6-12 maanden net zo effectief was als een behandeling van IUI met OS. Een afwachtend beleid bij paren met een goede kans op natuurlijke conceptie wordt niet altijd toegepast, wat leidt tot overbehandeling, onnodige complicaties en kosten. Een meerlingzwangerschap is een veel voorkomende complicatie van vruchtbaarheidsbehandelingen en wordt geassocieerd met een hogere morbiditeit en mortaliteit bij zowel moeders als pasgeborenen.
Het is onduidelijk hoe dit afwachtend beleid bij paren met een goede kans op natuurlijke conceptie is geïmplementeerd in Nederland. Twee grote prospectieve cohortstudies suggereren een slechte implementatie. Dit proefschrift heeft onder andere als doel meer inzicht te krijgen in de implementatie van een afwachtend beleid bij paren met een goede kans op natuurlijke conceptie en te evalueren hoe dit verbeterd kan worden. Om deze implementatie te optimaliseren is een systematische aanpak nodig: het verwerven van gegevens van de huidige praktijk; een analyse van belemmerende en bevorderende factoren voor de implementatie; de ontwikkeling van een implementatiestrategie en ten slotte een evaluatie van deze implementatiestrategie. In dit proefschrift is deze systematische aanpak gebruikt om inzicht te krijgen in de mogelijkheden om de uitvoering van dit afwachtend beleid bij paren met een goede kans op natuurlijke conceptie te verbeteren.

Naast deze implementatiestudie hebben we in dit proefschrift de toepasbaarheid van de prognose op natuurlijke conceptie verder geëvalueerd. Deze evaluatie bestaat uit twee delen. Ten eerste hebben we twee selectiemethoden voor vruchtbaarheidsbehandelingen

vergeleken: de in Nieuw Zeeland gebruikte “CPAC score” en het gevalideerde prognostische model van Hunault. In Nieuw-Zeeland worden vruchtbaarheidsbehandelingen alleen vergoed als paren een lage kans hebben op natuurlijke conceptie volgens bepaalde klinische en sociale criteria. Deze criteria staan bekend als de “Clinical Priority Access Criteria” (CPAC-score). In Nederland worden paren geselecteerd voor behandeling op basis van hun kans op natuurlijke conceptie, berekend met het gevalideerde prognostisch model van Hunault. In deze studie werd de kwaliteit van beide selectiemethoden vergeleken in een cohort uit Nieuw Zeeland bestaande uit 663 subfertiele paren.
Ten tweede hebben we geprobeerd meer inzicht krijgen in de selectieve capaciteiten van het prognostisch model van Hunault dat de kans op natuurlijke conceptie voorspelt. Op dit moment is het onduidelijk of dit prognostische model de arts kan helpen om de juiste behandeling te kiezen voor subfertiele paren met onverklaarde of milde mannelijke subfertiliteit. In dit laatste gedeelte van het proefschrift hebben we geëvalueerd of prognose kan helpen patiënten te selecteren voor een specifieke behandeling. We hebben dit probleem aangepakt door individuele patiëntgegevens van gepubliceerde gerandomiseerde studies te verzamelen en te analyseren. Auteurs van gepubliceerde gerandomiseerde studies die een afwachtend beleid (EM), intracervical inseminatie (ICI), IUI, alle drie met of zonder ovariële stimulatie en IVF vergeleken bij paren met onverklaarde of mannelijke subfertiliteit, werden benaderd en gevraagd hun oorspronkelijke data te delen. In alle datasets hebben we de kans op natuurlijke conceptie voor elk koppel berekend met het gevalideerde prognostische model. Vervolgens hebben we geanalyseerd of deze prognose een significant effect had op de uitkomst van de behandeling.

Hoofdstuk 1 geeft een overzicht en een beschrijving van de doelstellingen van dit proefschrift.

Hoofdstuk 2 beschrijft de resultaten van een cohortstudie waarin we risicofactoren onderzochten voor het niet naleven van afwachtend beleid bij paren met een goede prognose. Paren met een milde mannelijke, onverklaarde en cervicale subfertiliteit werden opgenomen in deze cohortstudie. Als de kans op natuurlijke conceptie binnen 12 maanden volgens het prognostisch model van Hunault ≥40% was, adviseerde het studieprotocol een afwachtend beleid gedurende 6-12 maanden. Multivariabele logistische regressie-analyse werd gebruikt om de patiënt en de klinische kenmerken die geassocieerd waren met het niet naleven van dit afwachtende beleid te identificeren. In totaal werden 3021 paren opgenomen in dit cohort waarvan 1130 (38%) een kans van ≥40% hadden op natuurlijke conceptie. Follow-up was beschikbaar voor 1020 (90%) paren. Tweehonderdveertien (21%) paren waren begonnen met een behandeling tussen zes en twaalf maanden en 153 (15%) binnen zes maanden. Een hogere leeftijd van de vrouw en een langere duur van de subfertiliteit waren geassocieerd met de behandeling binnen zes maanden (OR: 1,06, 95% CI: 1,01-1,1, OR: 1,4, 95% CI: 1,1-1,8 respectievelijk). Een fertiliteitsarts in een klinisch team verminderde het risico van de behandeling binnen zes maanden (OR: 0,62, 95% CI: 0,39-0,99). Wij concludeerden dat er bij

paren met een gunstige prognose op natuurlijke conceptie een aanzienlijke overbehandeling is, vooral als de vrouw ouder is en de duur van de subfertiliteit langer. De aanwezigheid van een fertiliteitsarts in een kliniek kan te vroege behandeling voorkomen.

Hoofdstuk 3 beschrijft een kwalitatieve studie waarin de belemmerende en bevorderende factoren van een afwachtend beleid bij paren met een goede prognose bij subfertiele paren en professionals werden geïdentificeerd. Deze belemmerende en bevorderende factoren werden geïdentificeerd door middel van semigestructureerde diepte-interviews met 21 subfertiele patiënten die een afwachtend beleid hadden gekregen. Daarnaast werden drie focusgroep interviews gehouden met 21 professionals werkzaam in de fertiliteit. De primaire uitkomstmaat waren de geïdentificeerde belemmerende en bevorderende factoren die de uitvoering van een afwachtend beleid bij een goede prognose beïnvloeden. Bij de subfertiele paren waren de belangrijkste barrières een gebrek aan vertrouwen in natuurlijke conceptie, het idee dat een afwachtend beleid tijdsverspilling is, verkeerde verwachtingen voorafgaand aan het eerste consult, het niet begrijpen van de reden van het afwachtend beleid en een overschatting van slagingspercentages van behandelingen. Zowel koppels als professionals zagen het gebrek aan patiënt informatiemateriaal als een belangrijke barrière. Onder de professionals was beperkte kennis over prognostische modellen één van de belangrijkste barrières. Eén van de belangrijkste bevorderende factor genoemd door de professionals was het beter sturen van de verwachtingen van de patiënt.

Hoofdstuk 4 beschrijft een landelijk onderzoek naar de prevalentie van de in hoofdstuk 3 geïdentificeerde belemmerende en bevorderende factoren. Hiernaast wordt in dit hoofdstuk geëvalueerd welke factoren invloed hebben op de waardering van patiënten op het afwachtend beleid en de naleving door professionals op het afwachtend beleid. Twee vragenlijsten werden ontwikkeld op basis van de in hoofdstuk 3 vastgestelde factoren en naar 195 koppels en 167 professionals gestuurd. Multivariabele analyse werd uitgevoerd om te evalueren welke factoren invloed hebben op de waardering van patiënten op het afwachtend beleid en de naleving door professionals van het afwachtend beleid. In totaal reageerden 118 (61%) paren en 117 (70%) professionals. De gemiddelde waardering die patiënten gaven aan het afwachtend beleid bij een goede prognose op een 10-punts schaal was 5,7. Patiënten die het afwachtend beleid lager waardeerden hadden meer behoefte aan patiëntinformatie ($p = 0,047$). De professionals rapporteerden een gemiddelde naleving van een afwachtend beleid bij een goede prognose van 63%. De naleving was hoger wanneer professionals fertiliteitsartsen waren ($p = 0,041$).

Hoofdstuk 5 beschrijft het protocol van een lopende evaluatie van een implementatie-strategie ter bevordering van een afwachtend beleid bij subfertiele paren met een goede prognose. De huidige implementatie van een afwachtend beleid bij paren met een goede prognose is niet optimaal (hoofdstuk 2). Op basis van de belemmerende en bevorderende

factoren die werden geïdentificeerd onder professionals en subfertiele paren in hoofdstuk 3 en 4, hebben we een implementatiestrategie ontwikkeld. De implementatiestrategie richt zich op subfertiele paren en hun zorgverleners d.w.z. huisartsen, fertiliteitsartsen en gynaecologen. Deze implementatiestrategie richt zich op drie niveaus: (1) Patiëntniveau: ontwikkelen van een informatiefolder en een informatieve website, (2) Professioneel niveau: audit en feedback, educatieve bezoeken aan ziekenhuizen, communicatietraining en toegang tot een digitale versie van het prognostische model van Hunault, (3) Organisatorisch niveau: een lokaal protocol gebaseerd op de richtlijn. In een cluster gerandomiseerde studie worden 25 klinieken en de hieraan gelieerde huisartsenpraktijken gerandomiseerd tussen deze implementatiestrategie en "care as usual". Het effect van deze implementatiestrategie zal worden geëvalueerd door een pre-en post-randomisatie dataverzameling. Hiernaast zal er een proces-analyse en een kosten-analyse plaatsvinden.

Hoofdstuk 6 beschrijft de kwaliteit van twee selectiemethoden om paren te selecteren voor een vruchtbaarheidsbehandeling: de in Nieuw Zeeland gebruikte CPAC-score en het prognostische model van Hunault. In Nieuw-Zeeland is vergoeding voor een vruchtbaarheidsbehandeling alleen beschikbaar voor subfertiele vrouwen met een lage kans op natuurlijke conceptie, gebaseerd op klinische en sociale criteria die bekend staan als de "Clinical Priority Access Criteria" (CPAC-score). In deze studie werd deze CPAC score vergeleken met het gevalideerde prognostisch model van Hunault dat in de Nederlandse richtlijn Onverklaarde Subfertiliteit wordt geadviseerd om patiënten te selecteren voor een behandeling. Voor deze vergelijking hebben we een cohort van 663 subfertiele paren gebruikt uit Nieuw-Zeeland. Van deze 663 paren hadden 249 (38%) paren een onverklaarde subfertiliteit. Van 246 vrouwen waren follow-up gegevens beschikbaar, hiervan hadden 143 (58%) paren een levendgeborene of doorgaande zwangerschap tijdens de follow-up periode van 4-5 jaar; 65 (26%) na vruchtbaarheidsbehandelingen en 78 (32%) na natuurlijke conceptie. Er waren 100 paren (41%) die een Hunault score hadden van <30%, de behandelgrens volgens de Nederlandse richtlijn. Zesendertig paren (15%) hadden een CPAC-score van> 65, de behandelgrens in Nieuwe Zeeland. In totaal waren er 69 paren (28%) die een behandeling zouden krijgen volgens de Nederlandse richtlijn maar niet volgens richtlijn in Nieuw Zeeland. De kappacoëfficiënt, als een mate van overeenstemming tussen de twee scores en hun behandelgrens was 0.30, duidend op een matige overeenstemming. Het discriminerende vermogen van beide selectiemethoden was vergelijkbaar (AUC: 0.63), maar de Hunault score presteerde beter in de kalibratie.

Hoofdstuk 7 beschrijft het studieprotocol van een individuele patiënt data (IPD) analyse van de relatie tussen het prognostische profiel van subfertiele paren en het effect hiervan op de behandeluitkomst. De meeste tot nu toe gepubliceerde studies die behandelstrategieën voor paren met een onverklaarde of mannelijke subfertiliteit hebben onderzocht, hebben prognose niet meegenomen in de evaluatie van het behandeleffect. Het zou kunnen dat

de individuele prognose van een paar het effect van de behandeling beïnvloedt. Met deze IPD-analyse kunnen we rekening houden met deze prognostische factoren en het effect hiervan op de behandeluitkomst evalueren. Data van gepubliceerde studies werden verzameld om deze IPD-analyse uit te voeren. De behandelingen die zijn geëvalueerd zijn ovariële stimulatie met getimede coïtus, Intra Cervicale Inseminatie (ICI) en IUI beide met en zonder ovariële stimulatie en IVF. Op basis van eerdere systematische reviews en een nieuw literatuuronderzoek werden studies geïncludeerd. Auteurs werden uitgenodigd om hun oorspronkelijke geanonimiseerde data te delen. De gegevens werden beoordeeld op validiteit, kwaliteit en volledigheid. De prognose van het individuele paar werd berekend en het effect van prognose op de behandeluitkomst werd geanalyseerd met logistische regressie analyse.

Hoofdstuk 8 rapporteert de resultaten van de in hoofdstuk 7 beschreven studie. Data van 8 gerandomiseerde studies met in totaal 2.550 paren werden verkregen. In drie studies bleken de meer ingrijpende behandelstrategieën minder effectief bij paren met een hoge kans op natuurlijke conceptie, maar dit verschil was niet significant (p-waarde voor interactie 0,71, 0,31 en 0,19). In één studie leidden alle strategieën met ovariële stimulatie (ICI en IUI) tot hogere zwangerschapcijfers dan bij de niet gestimuleerde strategieën, ongeacht prognose, maar ten koste van een hoog percentage meerlingzwangerschappen van van 23 en 30%. In twee studies leken de meer ingrijpende behandelstrategieën effectiever bij paren met een goede prognose, maar dit verschil was niet statistisch significant (p-waarde voor interactie 0,38 en 0,68). De enige studie waarin een afwachtend beleid werd vergeleken met IVF includeerde 38 paren hetgeen te weinig is voor een nauwkeurige schatting. Onze analyses excluderen grote differentiële effecten van de prognose op de effectiviteit van vruchtbaarheidsbehandelingen.

List of publications

LIST OF PUBLICATIONS:

1. Tailored expectant management: risk factors for non-adherence
   van den Boogaard NM, Oude Rengerink K, Steures P, Bossuyt PM, Hompes PG, van der Veen F, Mol BW, van der Steeg JW.
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About the author

ABOUT THE AUTHOR

Noortje Moniek van den Boogaard was born on the 14th of september 1981 in Eindhoven, The Netherlands. After she graduated the gymnasium at the Maurick college in Vught in 1999, she went travelling for a year. Subsequently she studied psychology at the University of Utrecht. In 2001 she started medical school at the Free University of Amsterdam. She performed two internships in South Africa and in 2008 she graduated.

Her first job as a medical doctor was at the obstetrics and gynaecology department of the Spaarne hospital in Hoofddorp under the supervision of Dr. M.H. Emanuel and Dr. I. de Graaf. After a year of clinical work she started her PhD at the Academic Medical Centre (AMC) of Amsterdam and the Free University of Amsterdam in 2009. The project was supervised by Prof. dr. F. van der Veen, Prof. dr. B.W. Mol, Dr. P.G.A. Hompes en Dr. W.N. Nelen. and resulted in this thesis. Next to her work on this thesis she worked in this period as a fertility doctor at the Centre for Reproductive Medicine of the AMC.

In januari 2012 she started her residency Obstetrics and Gynaecology at the Diakonessen-ziekenhuis in Utrecht under supervision of Dr. Scholten and Dr. Schuitemaker.